# WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Friday, March 12, 2004

| Hide? | Set Name | Query | Hit Count |
|---|---|---|---|
| | | *DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ* | |
| ☐ | L7 | (insulin-like growth factor-1 or IGF-1) same crystal$7 | 13 |
| | | *DB=PGPB; THES=ASSIGNEE; PLUR=YES; OP=ADJ* | |
| ☐ | L6 | US-20020165155-A1.did. | 1 |
| ☐ | L5 | US-20020165155-A1.did. | 1 |
| | | *DB=EPAB; THES=ASSIGNEE; PLUR=YES; OP=ADJ* | |
| ☐ | L4 | WO-200264627-A2.did. | 0 |
| ☐ | L3 | EP-1358209-A2.did. | 0 |
| | | *DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ* | |
| ☐ | L2 | l1 and (igf-1 same cryst$7) | 5 |
| ☐ | L1 | human same (insulin-like growth factor-1 or IGF-1) and crystal$7 | 584 |

END OF SEARCH HISTORY

# Hit List

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

**Search Results** - Record(s) 1 through 5 of 5 returned.

☐ 1. Document ID: US 20030148968 A1

**Using default format because multiple data bases are involved.**

L2: Entry 1 of 5 File: PGPB Aug 7, 2003

PGPUB-DOCUMENT-NUMBER: 20030148968
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030148968 A1

TITLE: Techniques and compositions for treating cardiovascular disease by in vivo gene delivery

PUBLICATION-DATE: August 7, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | COUNTRY | RULE-47 |
|---|---|---|---|---|
| Hammond, H. Kirk | La Jolla | CA | US | |
| Dillmann, Wolfgang | Solana Beach | CA | US | |
| Giordano, Frank J. | Madison | CT | US | |

US-CL-CURRENT: 514/44; 604/500

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw D

☐ 2. Document ID: US 20030092631 A1

L2: Entry 2 of 5 File: PGPB May 15, 2003

PGPUB-DOCUMENT-NUMBER: 20030092631
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030092631 A1

TITLE: IGF antagonist peptides

PUBLICATION-DATE: May 15, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | COUNTRY | RULE-47 |
|---|---|---|---|---|
| Deshayes, Kurt D. | San Francisco | CA | US | |
| Lowman, Henry B. | El Granada | CA | US | |
| Schaffer, Michelle L. | Cambridge | CA | GB | |

Sidhu, Sachdev S. San Francisco US

US-CL-CURRENT: 514/14; 530/326

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

---

☐ 3. Document ID: US 20020165155 A1

L2: Entry 3 of 5 File: PGPB Nov 7, 2002

PGPUB-DOCUMENT-NUMBER: 20020165155
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020165155 A1

TITLE: Crystallization of IGF-1

PUBLICATION-DATE: November 7, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | COUNTRY | RULE-47 |
|---|---|---|---|---|
| Schaffer, Michelle | Cambridge | CA | GB | |
| Ultsch, Mark | Mill Valley | CT | US | |
| Vajdos, Felix | Ledyard | | US | |

US-CL-CURRENT: 514/12; 530/350, 702/19

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

---

☐ 4. Document ID: US 6124259 A

L2: Entry 4 of 5 File: USPT Sep 26, 2000

US-PAT-NO: 6124259
DOCUMENT-IDENTIFIER: US 6124259 A

TITLE: Method for treating ophthalmic disorders with IGFBP

DATE-ISSUED: September 26, 2000

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Delmage; Michael J. | Scotts Valley | CA | | |
| Sommer; Andreas | Pleasanton | CA | | |

US-CL-CURRENT: 514/12; 435/69.1, 530/324, 530/350

ABSTRACT:

This is a method for treating ophthalmic disorders associated with an excess of IGF-I or IGF-II. The method comprises administering individuals with an IGF excess

insulin-like growth factor binding protein (IGFBP). The preferred form is IGFBP-3.

14 Claims, 0 Drawing figures
Exemplary Claim Number: 1



☐ 5. Document ID: EP 1358209 A2, WO 200264627 A2, US 20020165155 A1

L2: Entry 5 of 5 File: DWPI Nov 5, 2003

DERWENT-ACC-NO: 2002-723170
DERWENT-WEEK: 200377


TITLE: Crystal formed by insulin-like growth factor-1, IGF-1, useful for treating agonist disorders, diffracts x-ray radiation to produce a diffraction pattern representing the three-dimensional structure of IGF-1

INVENTOR: SCHAFFER, M; ULTSCH, M ; VAJDOS, F

PRIORITY-DATA: 2001US-287072P (April 27, 2001), 2001US-267977P (February 9, 2001), 2002US-0066009 (February 1, 2002)

PATENT-FAMILY:

| PUB-NO | PUB-DATE | LANGUAGE | PAGES | MAIN-IPC |
|---|---|---|---|---|
| EP 1358209 A2 | November 5, 2003 | E | 000 | C07K014/65 |
| WO 200264627 A2 | August 22, 2002 | E | 067 | C07K014/65 |
| US 20020165155 A1 | November 7, 2002 | | 000 | A61K038/18 |

INT-CL (IPC): A61 K 38/18; C07 K 14/475; C07 K 14/65; C30 B 29/58; G01 N 33/48; G01 N 33/50; G06 F 19/00

ABSTRACTED-PUB-NO: WO 200264627A
BASIC-ABSTRACT:

NOVELTY - A crystal (I) formed by insulin-like growth factor-1 (IGF-1) that diffracts x-ray radiation to produce a diffraction pattern representing the three-dimensional structure of IGF-1, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a composition (II) comprising (I), and a carrier;

(2) crystallizing (M1) IGF-1, involves mixing an aqueous solution comprising IGF-1 with a reservoir solution comprising a precipitant to form a mixed volume, and crystallizing the mixed volume;

(3) crystalline IGF-1 (III) produced by (M1);

(4) identifying (M2) indirect agonists of IGF-1, involves:

(a) comparing the ability of N,N-bis(3-D-gluconamidopropyl)- deoxycholamine to inhibit binding of IGF binding protein 1 (IGFBP-1) or IGFBP-3 to IGF-1 with the

ability of a candidate indirect agonist of IGF-1 to inhibit binding, and determining whether the candidate agonist inhibits such binding as well as N,N-bis (3-D-gluconamidopropyl)-deoxychol- amine; or

(b) co-crystallizing a candidate direct agonist IGF-1 with IGF-1 to form a co-crystalline structure and determining if the candidate agonist binds to one or both of two patches on IGF-1, where one patch has the amino acid residues Glu3, Thr4, Leu5, Asp12, Ala13, Phe16, Val17, Cys47, Ser51, Cys52, Asp53, Leu54 and Leu57, and the second patch has the amino acid residues Val11, Gln15, Phe23, Phe25, Asn26, Val44, Phe49 and Arg55, and binding occurs if there is a contact between each listed amino acid residue of a given patch and the candidate agonist that is less than or equal to 6 Angstrom in the co-crystalline structure;

(5) a co-crystalline complex (IV) of IGF-1 and N,N-bis(3-D-gluconamidoprop- yl)-deoxycholamine;

(6) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data that, when read by an appropriate machine, displays a three-dimensional representation of a crystal of a molecule comprising IGF-1;

(7) an IGF-1 crystal (V) with the structural coordinates of fully defined in the specification;

(8) identifying (M3) IGF-1 agonists or antagonists, involves crystallizing IGF-1 to form IGF-1 crystals containing a group of amino acid residues defining an IGF-1 receptor-binding region, irradiating the IGF-1 crystals to obtain a diffraction pattern of the IGF-1 crystals, determining a three-dimensional structure of IGF-1 from the diffraction pattern, and identifying an IGF-1 agonist or antagonist having a three-dimensional structure that functionally duplicates essential IGF receptor-binding, solvent-accessible residues presenting the three-dimensional structure of the IGF-1 receptor-binding region, and has altered signal transduction capacity to IGF-1-responsive cells, as compared to IGF-1;

(9) identifying (M4) a peptidomimetic that binds IGF-1 and blocks binding of an IGFBP or a receptor that binds to IGF-1, involves searching a molecular structure database with the structural parameters or structural coordinates fully defined in the specification, and selecting a molecule from the database that mimics the structural parameters or coordinates;

(10) determining (M5) a portion of a three-dimensional structure of a molecular complex comprising IGF-1, involves determining the structural coordinates of a crystal of IGF-1, calculating phases from the structural coordinates, calculating an electron density map from the obtained phases, and determining the structure of a portion of the complex based on the electron density map;

(11) evaluating (M6) the ability of a chemical entity to associate with IGF-1 or its complex, by employing computational or experimental unit to perform a fitting operation between the chemical entity and the IGF-1 or its complex, to obtain data related to the association, and analyzing the obtained data to determine the characteristics of the association between the chemical entity and the IGF-1 or its complex;

(12) a chemical entity (VI) identified by the above method, that interferes with in vivo or in vitro association between IGF-1 and its receptor or between IGF-1 and one of its binding proteins, or associates with a binding site on IGF-1;

(13) determining (M7) a three-dimensional structure of IGF-1, involves crystallizing the IGF-1, irradiating the crystalline IGF-1 to obtain a diffraction pattern characteristic of the crystalline IGF-1, and transforming the diffraction

pattern into the three-dimensional structure of IGF-1; and

(14) a heavy-atom derivative (VII) of a crystallized form of IGF-1.

ACTIVITY - Antidiabetic; Anorectic; Cardiant; Anti-HIV; Immunostimulant.

MECHANISM OF ACTION - Agonist of IGF-1.

No biological data given.

USE - (I) including an IGF-1 receptor-binding region, is useful for identifying compounds having structures that interact with the receptor-binding region of the three-dimensional structure of IGF-1 and function as an IGF-1 agonist or antagonist. (II) is useful for treating a mammal, especially human suffering from an agonist disorder such as diabetes, obesity, heart dysfunction, acquired immunodeficiency syndrome (AIDS)-related wasting, kidney disorder, neurological disorder, whole body growth disorder or immunological disorder. (III) is useful for computationally or experimentally evaluating a chemical entity to obtain information about its association with a binding site of IGF-1. (M4) is useful for designing a compound that mimics the 3-dimensional surface structure of IGF-1 (claimed). (I) is useful as standard or control in a diagnosing setting, for e.g. as a molecular weight marker or ELISA, radioassay, radioreceptor assay control; and studying binding properties of IGF-1, IGFBPs and IGF-1 receptors. (III) is useful for designing chemical entities that bind to or associate with IGF-1, and for altering physical properties of the chemical entities in different ways. (IV) and indirect agonist identified by (M2) are useful for treating the above mentioned agonist disorders, including immuno-deficiencies, Turner's syndrome, insulin resistance and necrosis. (III) is useful for solving the crystal structures of mutants, co-complexes, or crystalline form of any other molecule homologous to or capable of associating with a portion of IGF-1.

DESCRIPTION OF DRAWING(S) - The figure shows a ribbon diagram of IGF-1 showing the backbone fold.





| Terms | Documents |
|---|---|
| L1 and (igf-1 same cryst$7) | 5 |

# Hit List

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

**Search Results** - Record(s) 1 through 13 of 13 returned.

☐ 1. Document ID: US 20030148968 A1

**Using default format because multiple data bases are involved.**

L7: Entry 1 of 13 File: PGPB Aug 7, 2003

PGPUB-DOCUMENT-NUMBER: 20030148968
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030148968 A1

TITLE: Techniques and compositions for treating cardiovascular disease by in vivo gene delivery

PUBLICATION-DATE: August 7, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | COUNTRY | RULE-47 |
|---|---|---|---|---|
| Hammond, H. Kirk | La Jolla | CA | US | |
| Dillmann, Wolfgang | Solana Beach | CA | US | |
| Giordano, Frank J. | Madison | CT | US | |

US-CL-CURRENT: 514/44; 604/500

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 2. Document ID: US 20030124197 A1

L7: Entry 2 of 13 File: PGPB Jul 3, 2003

PGPUB-DOCUMENT-NUMBER: 20030124197
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030124197 A1

TITLE: Compositions and methods for improving integrity of compromised body passageways and cavities

PUBLICATION-DATE: July 3, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | COUNTRY | RULE-47 |
|---|---|---|---|---|
| Signore, Pierre E. | Vancouver | | CA | |
| Machan, Lindsay S. | Vancouver | | CA | |

US-CL-CURRENT: 424/499; 424/501, 514/283, 514/449, 514/54, 514/55

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

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☐ 3. Document ID: US 20030092631 A1

L7: Entry 3 of 13 File: PGPB May 15, 2003

PGPUB-DOCUMENT-NUMBER: 20030092631
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030092631 A1

TITLE: IGF antagonist peptides

PUBLICATION-DATE: May 15, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | COUNTRY | RULE-47 |
|---|---|---|---|---|
| Deshayes, Kurt D. | San Francisco | CA | US | |
| Lowman, Henry B. | El Granada | CA | US | |
| Schaffer, Michelle L. | Cambridge | CA | GB | |
| Sidhu, Sachdev S. | San Francisco | | US | |

US-CL-CURRENT: 514/14; 530/326

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

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☐ 4. Document ID: US 20030054973 A1

L7: Entry 4 of 13 File: PGPB Mar 20, 2003

PGPUB-DOCUMENT-NUMBER: 20030054973
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030054973 A1

TITLE: Methods and compositions for the repair and/or regeneration of damaged myocardium

PUBLICATION-DATE: March 20, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | COUNTRY | RULE-47 |
|---|---|---|---|---|
| Anversa, Piero | New York | NY | US | |

US-CL-CURRENT: 514/1; 435/372

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

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☐ 5. Document ID: US 20030050262 A1

L7: Entry 5 of 13 File: PGPB Mar 13, 2003

PGPUB-DOCUMENT-NUMBER: 20030050262
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030050262 A1

TITLE: Inhibition of neurodegeneration

PUBLICATION-DATE: March 13, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | COUNTRY | RULE-47 |
|---|---|---|---|---|
| Wands, Jack R. | Waban | MA | US | |
| Monte, Suzanne M. de la | East Greenwich | RI | US | |

US-CL-CURRENT: 514/44; 435/368

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

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☐ 6. Document ID: US 20030027202 A1

L7: Entry 6 of 13 File: PGPB Feb 6, 2003

PGPUB-DOCUMENT-NUMBER: 20030027202
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030027202 A1

TITLE: Methods of screening compounds for bioactivity in organized tissue

PUBLICATION-DATE: February 6, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | COUNTRY | RULE-47 |
|---|---|---|---|---|
| Vandenburgh, Herman H. | Providence | RI | US | |
| Valentini, Robert F. | Cranston | RI | US | |

US-CL-CURRENT: 435/6; 435/4, 435/7.21

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

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☐ 7. Document ID: US 20020165155 A1

L7: Entry 7 of 13 File: PGPB Nov 7, 2002

PGPUB-DOCUMENT-NUMBER: 20020165155
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020165155 A1

TITLE: Crystallization of IGF-1

PUBLICATION-DATE: November 7, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | COUNTRY | RULE-47 |
|---|---|---|---|---|
| Schaffer, Michelle | Cambridge | CA | GB | |
| Ultsch, Mark | Mill Valley | CT | US | |
| Vajdos, Felix | Ledyard | | US | |

US-CL-CURRENT: 514/12; 530/350, 702/19

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 8. Document ID: US 20020106627 A1

L7: Entry 8 of 13 File: PGPB Aug 8, 2002

PGPUB-DOCUMENT-NUMBER: 20020106627
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020106627 A1

TITLE: METHODS OF SCREENING COMPOUNDS FOR BIOACTIVITY IN ORGANIZED TISSUE

PUBLICATION-DATE: August 8, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | COUNTRY | RULE-47 |
|---|---|---|---|---|
| VANDENBURGH, HERMAN H. | PROVIDENCE | RI | US | |
| VALENTINI, ROBERT F. | CRANSTON | RI | US | |

US-CL-CURRENT: 435/4

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 9. Document ID: US 20020022055 A1

L7: Entry 9 of 13 File: PGPB Feb 21, 2002

PGPUB-DOCUMENT-NUMBER: 20020022055
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020022055 A1

TITLE: Composition and methods for immproving integrity of compromised body passageways and cavities

PUBLICATION-DATE: February 21, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | COUNTRY | RULE-47 |
|---|---|---|---|---|
| Signore, Pierre E | Vancouver British Columbia | | CA | |

US-CL-CURRENT: 424/486

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 10. Document ID: US 6124259 A

L7: Entry 10 of 13 File: USPT Sep 26, 2000

US-PAT-NO: 6124259
DOCUMENT-IDENTIFIER: US 6124259 A

TITLE: Method for treating ophthalmic disorders with IGFBP

DATE-ISSUED: September 26, 2000

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Delmage; Michael J. | Scotts Valley | CA | | |
| Sommer; Andreas | Pleasanton | CA | | |

US-CL-CURRENT: 514/12; 435/69.1, 530/324, 530/350

ABSTRACT:

This is a method for treating ophthalmic disorders associated with an excess of IGF-I or IGF-II. The method comprises administering individuals with an IGF excess insulin-like growth factor binding protein (IGFBP). The preferred form is IGFBP-3.

14 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Draw. D

☐ 11. Document ID: WO 2064627 A2

L7: Entry 11 of 13 File: EPAB Aug 22, 2002

PUB-NO: WO002064627A2
DOCUMENT-IDENTIFIER: WO 2064627 A2
TITLE: CRYSTALLIZATION OF IGF-1

PUBN-DATE: August 22, 2002

INVENTOR-INFORMATION:

| NAME | COUNTRY |
|---|---|
| SCHAFFER, MICHELLE | |
| ULTSCH, MARK | |
| VAJDOS, FELIX | |

INT-CL (IPC): C07 K 14/65; C30 B 29/58

EUR-CL (EPC): C07K014/65

ABSTRACT:

Crystalline IGF-1 is provided along with a method for production thereof. Crystallizing IGF-1 comprises the steps of mixing an aqueous solution comprising IGF-1 with a reservoir solution comprising a precipitant to form a mixture; and crystallizing the mixture, optionally also recrystallizing and isolating the crystalline IGF-1. In addition, a method for identifying IGF-1 indirect agonists is provided using a detergent as a standard for the level of inhibition of binding of IGFBP-1 or IGFBP-3 to IGF-1 and/or using the coordinates of the binding pockets of IGF-1 to which a candidate indirect agonist binds for structure-based drug design.



☐ 12. Document ID: WO 9928347 A1

L7: Entry 12 of 13 File: EPAB Jun 10, 1999

PUB-NO: WO009928347A1
DOCUMENT-IDENTIFIER: WO 9928347 A1
TITLE: METHOD OF DESIGNING AGONISTS AND ANTAGONISTS TO IGF RECEPTOR

PUBN-DATE: June 10, 1999

INVENTOR-INFORMATION:

| NAME | COUNTRY |
|---|---|
| BENTLEY, JOHN DAVID | AU |
| COSGROVE, LEAH JANE | AU |
| FRENKEL, MAURICE JOHN | AU |
| GARRETT, THOMAS PETER JOHN | AU |
| LAWRENCE, LYNNE JEAN | AU |
| LOU, MEIZHEN | AU |
| LOVRECZ, GEORGE OSCAR | AU |
| MCKERN, NEIL MORETON | AU |
| TULLOCH, PETER ARCHIBALD | AU |
| WARD, COLIN WESLEY | AU |

INT-CL (IPC): C07 K 14/705; C07 K 14/71; G06 F 17/50; G06 F 19/00; G06 F 159/00
EUR-CL (EPC): C07K014/65

ABSTRACT:

CHG DATE=19990803 STATUS=O>The present invention relates to a method of designing compounds able to bind to a molecule of the insulin receptor family and to modulate the activity mediated by the receptor based on the 3-D structure coordinates of a IGF-1 receptor crystal of Figure 1.

☐ 13. Document ID: EP 1358209 A2, WO 200264627 A2, US 20020165155 A1

L7: Entry 13 of 13 File: DWPI Nov 5, 2003

DERWENT-ACC-NO: 2002-723170
DERWENT-WEEK: 200377


TITLE: Crystal formed by insulin-like growth factor-1, IGF-1, useful for treating agonist disorders, diffracts x-ray radiation to produce a diffraction pattern representing the three-dimensional structure of IGF-1

INVENTOR: SCHAFFER, M; ULTSCH, M ; VAJDOS, F

PRIORITY-DATA: 2001US-287072P (April 27, 2001), 2001US-267977P (February 9, 2001), 2002US-0066009 (February 1, 2002)

PATENT-FAMILY:

| PUB-NO | PUB-DATE | LANGUAGE | PAGES | MAIN-IPC |
|---|---|---|---|---|
| EP 1358209 A2 | November 5, 2003 | E | 000 | C07K014/65 |
| WO 200264627 A2 | August 22, 2002 | E | 067 | C07K014/65 |
| US 20020165155 A1 | November 7, 2002 | | 000 | A61K038/18 |

INT-CL (IPC): A61 K 38/18; C07 K 14/475; C07 K 14/65; C30 B 29/58; G01 N 33/48; G01 N 33/50; G06 F 19/00

ABSTRACTED-PUB-NO: WO 200264627A

BASIC-ABSTRACT:

NOVELTY - A crystal (I) formed by insulin-like growth factor-1 (IGF-1) that diffracts x-ray radiation to produce a diffraction pattern representing the three-dimensional structure of IGF-1, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a composition (II) comprising (I), and a carrier;

(2) crystallizing (M1) IGF-1, involves mixing an aqueous solution comprising IGF-1 with a reservoir solution comprising a precipitant to form a mixed volume, and crystallizing the mixed volume;

(3) crystalline IGF-1 (III) produced by (M1);

(4) identifying (M2) indirect agonists of IGF-1, involves:

(a) comparing the ability of N,N-bis(3-D-gluconamidopropyl)- deoxycholamine to inhibit binding of IGF binding protein 1 (IGFBP-1) or IGFBP-3 to IGF-1 with the ability of a candidate indirect agonist of IGF-1 to inhibit binding, and determining whether the candidate agonist inhibits such binding as well as N,N-bis (3-D-gluconamidopropyl)-deoxychol- amine; or

(b) co-crystallizing a candidate direct agonist IGF-1 with IGF-1 to form a co-crystalline structure and determining if the candidate agonist binds to one or both of two patches on IGF-1, where one patch has the amino acid residues Glu3, Thr4, Leu5, Asp12, Ala13, Phe16, Val17, Cys47, Ser51, Cys52, Asp53, Leu54 and Leu57, and

the second patch has the amino acid residues Val11, Gln15, Phe23, Phe25, Asn26, Val44, Phe49 and Arg55, and binding occurs if there is a contact between each listed amino acid residue of a given patch and the candidate agonist that is less than or equal to 6 Angstrom in the co-crystalline structure;

(5) a co-crystalline complex (IV) of IGF-1 and N,N-bis(3-D-gluconamidoprop- yl)-deoxycholamine;

(6) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data that, when read by an appropriate machine, displays a three-dimensional representation of a crystal of a molecule comprising IGF-1;

(7) an IGF-1 crystal (V) with the structural coordinates of fully defined in the specification;

(8) identifying (M3) IGF-1 agonists or antagonists, involves crystallizing IGF-1 to form IGF-1 crystals containing a group of amino acid residues defining an IGF-1 receptor-binding region, irradiating the IGF-1 crystals to obtain a diffraction pattern of the IGF-1 crystals, determining a three-dimensional structure of IGF-1 from the diffraction pattern, and identifying an IGF-1 agonist or antagonist having a three-dimensional structure that functionally duplicates essential IGF receptor-binding, solvent-accessible residues presenting the three-dimensional structure of the IGF-1 receptor-binding region, and has altered signal transduction capacity to IGF-1-responsive cells, as compared to IGF-1;

(9) identifying (M4) a peptidomimetic that binds IGF-1 and blocks binding of an IGFBP or a receptor that binds to IGF-1, involves searching a molecular structure database with the structural parameters or structural coordinates fully defined in the specification, and selecting a molecule from the database that mimics the structural parameters or coordinates;

(10) determining (M5) a portion of a three-dimensional structure of a molecular complex comprising IGF-1, involves determining the structural coordinates of a crystal of IGF-1, calculating phases from the structural coordinates, calculating an electron density map from the obtained phases, and determining the structure of a portion of the complex based on the electron density map;

(11) evaluating (M6) the ability of a chemical entity to associate with IGF-1 or its complex, by employing computational or experimental unit to perform a fitting operation between the chemical entity and the IGF-1 or its complex, to obtain data related to the association, and analyzing the obtained data to determine the characteristics of the association between the chemical entity and the IGF-1 or its complex;

(12) a chemical entity (VI) identified by the above method, that interferes with in vivo or in vitro association between IGF-1 and its receptor or between IGF-1 and one of its binding proteins, or associates with a binding site on IGF-1;

(13) determining (M7) a three-dimensional structure of IGF-1, involves crystallizing the IGF-1, irradiating the crystalline IGF-1 to obtain a diffraction pattern characteristic of the crystalline IGF-1, and transforming the diffraction pattern into the three-dimensional structure of IGF-1; and

(14) a heavy-atom derivative (VII) of a crystallized form of IGF-1.

ACTIVITY - Antidiabetic; Anorectic; Cardiant; Anti-HIV; Immunostimulant.

MECHANISM OF ACTION - Agonist of IGF-1.

No biological data given.

USE - (I) including an IGF-1 receptor-binding region, is useful for identifying compounds having structures that interact with the receptor-binding region of the three-dimensional structure of IGF-1 and function as an IGF-1 agonist or antagonist. (II) is useful for treating a mammal, especially human suffering from an agonist disorder such as diabetes, obesity, heart dysfunction, acquired immunodeficiency syndrome (AIDS)-related wasting, kidney disorder, neurological disorder, whole body growth disorder or immunological disorder. (III) is useful for computationally or experimentally evaluating a chemical entity to obtain information about its association with a binding site of IGF-1. (M4) is useful for designing a compound that mimics the 3-dimensional surface structure of IGF-1 (claimed). (I) is useful as standard or control in a diagnosing setting, for e.g. as a molecular weight marker or ELISA, radioassay, radioreceptor assay control; and studying binding properties of IGF-1, IGFBPs and IGF-1 receptors. (III) is useful for designing chemical entities that bind to or associate with IGF-1, and for altering physical properties of the chemical entities in different ways. (IV) and indirect agonist identified by (M2) are useful for treating the above mentioned agonist disorders, including immuno-deficiencies, Turner's syndrome, insulin resistance and necrosis. (III) is useful for solving the crystal structures of mutants, co-complexes, or crystalline form of any other molecule homologous to or capable of associating with a portion of IGF-1.

DESCRIPTION OF DRAWING(S) - The figure shows a ribbon diagram of IGF-1 showing the backbone fold.



| Terms | Documents |
|---|---|
| (insulin-like growth factor-1 or IGF-1) same crystal$7 | 13 |

```
=> s (insulin (3w) like growth factor-1 or IGF-1) and human and crystal?
L1          20 FILE MEDLINE
L2          16 FILE CAPLUS
L3          14 FILE SCISEARCH
L4           1 FILE LIFESCI
L5          14 FILE BIOSIS
L6          13 FILE EMBASE

TOTAL FOR ALL FILES
L7          78 (INSULIN (3W) LIKE GROWTH FACTOR-1 OR IGF-1) AND HUMAN AND CRYST
               AL?

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8          41 DUP REM L7 (37 DUPLICATES REMOVED)

=> d ibib abs 1-41

L8   ANSWER 1 OF 41     MEDLINE on STN                  DUPLICATE 1
ACCESSION NUMBER:   2003162191     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 12551896
TITLE:              Structural basis for dimerization of the Grb10 Src homology
                    2 domain. Implications for ligand specificity.
AUTHOR:             Stein Evan G; Ghirlando Rodolfo; Hubbard Stevan R
CORPORATE SOURCE:   Skirball Institute of Biomolecular Medicine and Department
                    of Pharmacology, New York University School of Medicine,
                    New York, New York 10016, USA.
CONTRACT NUMBER:    DK52916 (NIDDK)
SOURCE:             Journal of biological chemistry, (2003 Apr 11) 278 (15)
                    13257-64.
                    Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200307
ENTRY DATE:         Entered STN: 20030408
                    Last Updated on STN: 20030704
                    Entered Medline: 20030703
AB   Grb7, Grb10, and Grb14 are members of a distinct family of adapter
     proteins that interact with various receptor tyrosine kinases upon
     receptor activation.  Proteins in this family contain several modular
     signaling domains including a pleckstrin homology (PH) domain, a BPS
     (between PH and SH2) domain, and a C-terminal Src homology 2 (SH2) domain.
     Although SH2 domains are typically monomeric, we show that the Grb10 SH2
     domain and also full-length Grb10 gamma are dimeric in solution under
     physiologic conditions.  The crystal structure of the Grb10 SH2
     domain at 1.65-A resolution reveals a non-covalent dimer whose interface
     comprises residues within and flanking the C-terminal alpha helix, which
     are conserved in the Grb7/Grb10/Grb14 family but not in other SH2 domains.
     Val-522 in the BG loop (BG3) and Asp-500 in the EF loop (EF1) are
     positioned to interfere with the binding of the P+3 residue of a
     phosphopeptide ligand.  These structural features of the Grb10 SH2 domain
     will favor binding of dimeric, turn-containing phosphotyrosine sequences,
     such as the phosphorylated activation loops in the two beta subunits of
     the insulin and insulin-like growth
     factor-1 receptors.  Moreover, the structure suggests
     the mechanism by which the Grb7 SH2 domain binds selectively to pTyr-1139
     (pYVNQ) in Her2, which along with Grb7 is co-amplified in human
     breast cancers.

L8   ANSWER 2 OF 41  BIOSIS  COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER:   2003:256364  BIOSIS
DOCUMENT NUMBER:    PREV200300256364
TITLE:              Effects of prostaglandin analogues on human
                    ciliary muscle and trabecular meshwork cells.
AUTHOR(S):          Zhao, Xiujun; Pearson, Keri E.; Stephan, Dietrich A.;
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Russell, Paul [Reprint Author]
CORPORATE SOURCE: 6 Center Drive, MSC 2735, Bethesda, MD, 20892, USA
russellp@nei.nih.gov
SOURCE: IOVS, (May 2003) Vol. 44, No. 5, pp. 1945-1952. print.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 28 May 2003
Last Updated on STN: 30 Jun 2003

AB PURPOSE: To determine the effects of prostaglandin F2alpha analogues on gene expression of **human** ciliary muscle (HCM) and trabecular meshwork (HTM) cells. METHODS: Cultures of HCM and HTM cells were established from five different donors treated for 9 days with 10 mug/mL of either latanoprost (free acid) or prostaglandin F2alpha ethanolamide and compared with control cells. The mRNA from the cells of the five individual donors was pooled and analyzed by using gene microarrays. Gene expression changes were confirmed by either real-time PCR or relative quantitative PCR. RESULTS: Approximately 12 genes showed a twofold or greater change in expression under experimental conditions. Four of these may alter outflow. Aquaporin-1 and versican were down-regulated in the HCM, whereas IGF1 and fibroleukin were upregulated in HTM. Expression levels of TNFSF10 and promelanosome-concentrating hormone also increased in the treated HTM cells. The mRNA levels for the prostaglandin FP receptor were downregulated in the ciliary muscle cells. Optineurin and alphaB-**crystallin** levels remained unchanged, but myocilin in the HTM cells was decreased in some samples. CONCLUSIONS: Both analogues changed gene expression similarly in either HCM or HTM cells, but the changes appeared to be cell specific, perhaps indicating that other transcription factors are influential. Outflow of aqueous humor may be increased by the prostaglandin analogues by alterations in the extracellular matrix. Other changes may influence cellular metabolism, such as the increases in IGF1, tumor necrosis factor superfamily-10 and promelanosome-concentrating hormone.

L8 ANSWER 3 OF 41 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2003:735993 CAPLUS
DOCUMENT NUMBER: 140:159545
TITLE: Structure of apo, unactivated **insulin-like growth factor-1** receptor kinase at 1.5 .ANG. resolution
AUTHOR(S): Munshi, Sanjeev; Hall, Dawn L.; Kornienko, Maria; Darke, Paul L.; Kuo, Lawrence C.
CORPORATE SOURCE: Department of Structural Biology, Merck Research Laboratories, West Point, PA, 19486, USA
SOURCE: Acta Crystallographica, Section D: Biological Crystallography (2003), D59(10), 1725-1730
CODEN: ABCRE6; ISSN: 0907-4449
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **crystal** structure of **human** wild-type apo-unactivated **insulin-like growth factor-1** receptor kinase (I) was reported previously at 2.7 .ANG. resoln. In order to obtain a high-resoln. structure, a no. of variants of I were prepd. and screened for **crystn**. A double mutant with E1067A and E1069A substitutions within the kinase-insert region resulted in **crystals** that diffracted to 1.5 .ANG. resoln. Overall, the structure of mutant I was similar to that of the wild-type I structure, with the exception of the previously disordered kinase-insert region in the wild-type enzyme having become fixed. In addn., amino acid residues 947-952 at the N-terminus were well-defined in the mutant structure. The monomeric protein structure was found to be folded into 2 lobes connected by a hinge region, with the catalytic center situated at the interface of the 2 lobes. Two mols. of I in the asym. unit were assocd. as a dimer and 2 different types of dimers with their ATP-binding clefts either facing towards or away from each other were obsd. The current refined model consisted of a dimer and 635 water mols.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 41 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2003223629 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12746903
TITLE: One of two chondrocyte-expressed isoforms of cartilage intermediate-layer protein functions as an **insulin -like growth factor 1** antagonist.
AUTHOR: Johnson Kristen; Farley David; Hu Shou-Ih; Terkeltaub Robert
CORPORATE SOURCE: Department of Veterans Affairs Medical Center, San Diego, and University of California, San Diego, CA 92161, USA.
CONTRACT NUMBER: P01-AG-07996 (NIA)
SOURCE: Arthritis and rheumatism, (2003 May) 48 (5) 1302-14.
Journal code: 0370605. ISSN: 0004-3591.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20030515
Last Updated on STN: 20030531
Entered Medline: 20030530

AB OBJECTIVE: Aging and osteoarthritic (OA) cartilage commonly demonstrate enhanced expression of the large, transforming growth factor beta (TGFbeta)-inducible glycoprotein cartilage intermediate-layer protein (CILP) as well as enhanced extracellular inorganic pyrophosphate (PPi) that promotes the deposition of calcium pyrophosphate dihydrate **crystals**. In normal chondrocytes, TGFbeta induces elevated chondrocyte extracellular PPi. **Insulin-like growth factor 1** (**IGF-1**) normally blocks this response and reduces extracellular PPi. However, chondrocyte resistance to **IGF-1** is observed in OA and aging. Because CILP was reported to chromatographically fractionate with PPi-generating nucleotide pyrophosphatase phosphodiesterase (NPP) activity, it has been broadly assumed that CILP itself has NPP activity. Our objective was to directly define CILP functions and their relationship to **IGF-1** in chondrocytes. METHODS: Using primary cultures of articular chondrocytes from the knee, we defined the function of the previously described CILP (CILP-1) and of a recently described 50.6% identical protein that we designated the CILP-2 isoform. RESULTS: Both CILP isoforms were constitutively expressed by primary cultured articular chondrocytes, but only CILP-1 expression was detectable in cultured knee meniscal cartilage cells. Neither CILP isoform had intrinsic NPP activity. But CILP-1 blocked the ability of **IGF-1** to decrease extracellular PPi, an activity specific for the CILP-1 N-terminal domain. The CILP-1 N-terminal domain also suppressed **IGF-1**-induced (but not TGFbeta-induced) proliferation and sulfated proteoglycan synthesis, and it inhibited ligand-induced **IGF-1** receptor autophosphorylation. CONCLUSION: Two CILP isoforms are differentially expressed by chondrocytes. Neither CILP isoform exhibits PPi-generating NPP activity. But, increased expression of CILP-1, via N-terminal domain-mediated inhibitory effects of CILP-1 on chondrocyte **IGF-1** responsiveness, could impair chondrocyte growth and matrix repair and indirectly promote PPi supersaturation in aging and OA cartilage.

L8 ANSWER 5 OF 41 MEDLINE on STN
ACCESSION NUMBER: 2003344329 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12876554
TITLE: Growth factor induced activation of Rho and Rac GTPases and actin cytoskeletal reorganization in **human** lens epithelial cells.
AUTHOR: Maddala Rupalatha; Reddy Venkat N; Epstein David L; Rao Vasantha
CORPORATE SOURCE: Department of Ophthalmology, Duke University Medical Center, Durham, NC, USA.
CONTRACT NUMBER: EY 00484 (NEI)
EY013573 (NEI)
EY12201 (NEI)
SOURCE: Molecular vision [electronic resource], (2003 Jul 17) 9 329-36.
Journal code: 9605351. ISSN: 1090-0535.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030724
Last Updated on STN: 20030812
Entered Medline: 20030811

AB PURPOSE: To determine the involvement of the Rho GTPases-mediated signaling pathway in growth factor-stimulated actomyosin cytoskeletal organization and focal adhesion formation in lens epithelial cells. METHODS: Serum starved **human** lens epithelial cells (SRA01/04) were treated with different growth factors including epidermal growth factor (EGF), basic-fibroblast growth factor (b-FGF), platelet derived growth factor (PDGF), transforming growth factor beta (TGF-beta), **insulin-like growth factor 1** (**IGF-1**), lysophosphatidic acid (LPA), and thrombin. Growth factor stimulated activation of Rho and Rac GTPases were evaluated by GTP-loading pull-down assays. Changes in actin cytoskeletal organization and focal adhesions were determined by fluorescence staining using FITC-phalloidin and anti-vinculin antibody/rhodamine-conjugated secondary antibody, respectively. Fluorescence images were recorded using either confocal or fluorescence microscopy. RESULTS: Rho GTPase activity was significantly augmented in **human** lens epithelial cells treated with EGF, b-FGF, TGF-beta, **IGF-1**, and LPA. Rac GTPase activation, in contrast, was significantly enhanced in response to only EGF or b-FGF. Serum starved **human** lens epithelial cells exhibited a strong increase in cortical actin stress fibers and integrin-mediated focal adhesions in response to b-FGF, PDGF, TGF-beta, thrombin, and LPA. While EGF induced a striking increase in membrane ruffling and a marginal increase on focal adhesion formation, **IGF -1** had no effect on either. Pretreatment of lens epithelial cells with C3-exoenzyme (an irreversible inhibitor of Rho-GTPase), lovastatin (an isoprenylation inhibitor), or the Rho kinase inhibitor Y-27632 abolished the ability of the different growth factors to elicit actin stress fiber and focal adhesion formation. EGF induced membrane ruffling, however, was not suppressed by Y-27632 and C3-exoenzyme. CONCLUSIONS: These results demonstrate that different growth factors induce actin cytoskeleton reorganization and formation of cell-ECM interactions in lens epithelial cells and this response of growth factors appears to be mediated, at least in part, through the Rho/Rho kinase-mediated signaling pathway. The ability of growth factors to trigger activation of Rho and Rac GTPases along with actomyosin cytoskeletal reorganization and formation of focal adhesions might well play a crucial role in lens epithelial cell proliferation, migration, elongation and survival.

L8 ANSWER 6 OF 41 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:946319 CAPLUS
DOCUMENT NUMBER: 138:19948
TITLE: Mutants of IGF binding proteins comprising a complex of IGF and IGFBP polypeptides and use of the mutated IGFBPs in therapy and to identify antagonists
INVENTOR(S): Beisel, Hans-Georg; Demuth, Dirk; Engh, Richard; Holak, Tadeusz; Huber, Robert; Lang, Kurt; Schumacher, Ralf; Zeslawski, Wojciech
PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002098914 | A2 | 20021212 | WO 2002-EP6161 | 20020605 |
| WO 2002098914 | A3 | 20031211 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,

PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: EP 2001-112958 A 20010607

AB The present invention provides a **crystal** suitable for x-ray diffraction, comprising a complex of insulin-like growth factor I or II (IGF) and a polypeptide consisting of the amino acids 39-91 of IGFBP-1, the amino acids 55-107 of IGFBP-2, the amino acids 47-99 of IGFBP-3, the amino acids 39-91 of IGFBP-4, the amino acids 40-92 of IGFBP-5, or the amino acids 40-92 of IGFBP-6 or a fragment thereof consisting at least of the 9th to 12th cysteine of IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-4, or IGFBP-5 or at least of the 7th to 10th cysteine of IGFBP-6. Methods for the detn. of the at. coordinates of such a **crystal**; IGFBP mutants with enhanced binding affinity for IGF-I and/or IGF-II, and methods to identify and optimize small mols. which displace IGFs from their binding proteins are also disclosed. The mutants or small mols. can be used therapeutically.

L8 ANSWER 7 OF 41 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:637708 CAPLUS
DOCUMENT NUMBER: 137:190686
TITLE: **Crystallization** of **IGF-1**
INVENTOR(S): Schaffer, Michelle; Ultsch, Mark; Vajdos, Felix
PATENT ASSIGNEE(S): Genentech, Inc., USA
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002064627 | A2 | 20020822 | WO 2002-US3156 | 20020201 |
| WO 2002064627 | A3 | 20030731 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| US 2002165155 | A1 | 20021107 | US 2002-66009 | 20020201 |
| EP 1358209 | A2 | 20031105 | EP 2002-724908 | 20020201 |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.:
US 2001-267977P P 20010209
US 2001-287072P P 20010427
WO 2002-US3156 W 20020201

AB **Cryst. IGF-1** is provided along with a method for prodn. thereof. **Crystg. IGF-1** comprises the steps of mixing an aq. soln. comprising **IGF-1** with a reservoir soln. comprising a precipitant to form a mixt.; and **crystg.** the mixt., optionally also recrystg. and isolating the **cryst. IGF-1**. In addn., a method for identifying **IGF-1** indirect agonists is provided using a detergent as a std. for the level of inhibition of binding of IGFBP-1 or IGFBP-3 to **IGF-1** and/or using the coordinates of the binding pockets of **IGF-1** to which a candidate indirect agonist binds for structure-based drug design.

L8 ANSWER 8 OF 41 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:764471 CAPLUS
DOCUMENT NUMBER: 138:12365
TITLE: **Crystal** structure of the apo, unactivated **insulin-like growth**

**factor-1** receptor kinase.
Implication for inhibitor specificity
AUTHOR(S): Munshi, Sanjeev; Kornienko, Maria; Hall, Dawn L.; Reid, John C.; Waxman, Lloyd; Stirdivant, Steven M.; Darke, Paul L.; Kuo, Lawrence C.
CORPORATE SOURCE: Department of Structural Biology and Department of Cancer Research, Merck Research Laboratories, West Point, PA, 19486, USA
SOURCE: Journal of Biological Chemistry (2002), 277(41), 38797-38802
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The x-ray structure of the unactivated kinase domain of **insulin-like growth factor-1** receptor (IGFRK-0P) is reported here at 2.7 .ANG. resoln. IGFRK-0P was found to be composed of 2 lobes connected by a hinge region. The N-terminal lobe of the kinase was a twisted .beta.-sheet flanked by a single helix, and the C-terminal lobe comprised 8 .alpha.-helixes and 4 short .beta.-strands. The ATP-binding pocket and the catalytic center were found to reside at the interface of the 2 lobes. Despite the overall similarity to other receptor tyrosine kinases, 3 notable conformational modifications were obsd.: (1) this kinase adopted a more closed structure, with its 2 lobes rotated further toward each other; (2) the conformation of the proximal end of the activation loop (residues 1121-1129) was different; and (3) the orientation of the nucleotide-binding loop was altered. Collectively, these alterations led to a different ATP-binding pocket that might impact on inhibitor designs for IGFRK-0P. Two mols. of IGFRK-0P were seen in the asym. unit; they were assocd. as a dimer with their ATP-binding clefts facing each other. The ordered N-terminus of one monomer approached the active site of the other, suggesting that the juxtamembrane region of one mol. could come into close proximity to the active site of the other.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 41 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2002720350 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12483726
TITLE: Up-regulated expression of cartilage intermediate-layer protein and ANK in articular hyaline cartilage from patients with calcium pyrophosphate dihydrate **crystal** deposition disease.
AUTHOR: Hirose Jun; Ryan Lawrence M; Masuda Ikuko
CORPORATE SOURCE: Medical College of Wisconsin, Milwaukee.
CONTRACT NUMBER: AR-38656 (NIAMS)
AR-44862 (NIAMS)
SOURCE: Arthritis and rheumatism, (2002 Dec) 46 (12) 3218-29.
Journal code: 0370605. ISSN: 0004-3591.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20021218
Last Updated on STN: 20030111
Entered Medline: 20030110

AB OBJECTIVE: Excess accumulation of extracellular inorganic pyrophosphate (ePPi) in aged **human** cartilage is crucial in calcium pyrophosphate dihydrate (CPPD) **crystal** formation in cartilage matrix. Two sources of ePPi are ePPi-generating ectoenzymes (NTPPPH) and extracellular transport of intracellular PPi by ANK. This study was undertaken to evaluate the role of NTPPPH and ANK in ePPi elaboration, by investigating expression of NTPPPH enzymes (cartilage intermediate-layer protein [CILP] and plasma cell membrane glycoprotein 1 [PC-1]) and ANK in **human** chondrocytes from osteoarthritic (OA) articular cartilage containing CPPD **crystals** and without **crystals**.
METHODS: Chondrocytes were harvested from knee cartilage at the time of arthroplasty (OA with CPPD **crystals** [CPPD], n = 8; OA without **crystals** [OA], n = 10). Normal adult **human** chondrocytes

(n = 1) were used as a control. Chondrocytes were cultured with transforming growth factor betal (TGFbetal), which stimulates ePPi elaboration, and/or **insulin-like growth factor 1** (**IGF-1**), which inhibits ePPi elaboration. NTPPPH and ePPi were measured in the media at 48 hours. Media CILP, PC-1, and ANK were determined by dot-immunoblot analysis. Chondrocyte messenger RNA (mRNA) was extracted for reverse transcriptase-polymerase chain reaction to study expression of mRNA for CILP, PC-1, and ANK. NTPPPH and ANK mRNA and protein were also studied in fresh frozen cartilage. RESULTS: Basal ePPi elaboration and NTPPPH activity in conditioned media from CPPD chondrocytes were elevated compared with normal chondrocytes, and tended to be higher compared with OA chondrocytes. Basal expression of mRNA for CILP (chondrocytes) and ANK (cartilage) was higher in both CPPD chondrocytes and CPPD cartilage extract than in OA or normal samples. PC-1 mRNA was less abundant in CPPD chondrocytes and cartilage extract than in OA chondrocytes and extract, although the difference was not significant. CILP, PC-1, and ANK protein levels were similar in CPPD, OA, and normal chondrocytes or cartilage extracts. Both CILP and ANK mRNA expression and ePPi elaboration were stimulated by TGFbetal and inhibited by **IGF-1** in chondrocytes from all sources. CONCLUSION: CILP and ANK mRNA expression correlates with chondrocyte ePPi accumulation around CPPD and OA chondrocytes, and all respond similarly to growth factor stimulation. These findings suggest that up-regulated CILP and ANK expression contributes to higher ePPi accumulation from CPPD **crystal** -forming cartilage.

L8 ANSWER 10 OF 41 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:606024 BIOSIS
DOCUMENT NUMBER: PREV200200606024
TITLE: **Insulin-like growth factor-1** as a marker of mortality in intensive care unit acute renal failure patients.
AUTHOR(S): Mussi, Sergio M. [Reprint author]; Pereira, Roseli A. [Reprint author]; Burdmann, Emmanuel A.
CORPORATE SOURCE: Intensive Care Unit, Sao Jose do Rio Preto Medical School, Sao Jose do Rio Preto, Brazil
SOURCE: Journal of the American Society of Nephrology, (September, 2002) Vol. 13, No. Program and Abstracts Issue, pp. 690A. print.
Meeting Info.: Meeting of the American Society of Nephrology. Philadelphia, PA, USA. October 30-November 04, 2002. American Society of Nephrology.
CODEN: JASNEU. ISSN: 1046-6673.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Nov 2002
Last Updated on STN: 27 Nov 2002

L8 ANSWER 11 OF 41 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:256156 BIOSIS
DOCUMENT NUMBER: PREV200200256156
TITLE: Insulin-like growth factor system components in relation to erythropoietin therapy and bone metabolism in dialyzed patients and kidney transplant recipients.
AUTHOR(S): Malyszko, Jolanta [Reprint author]; Wolczynski, Slawomir; Zbroch, Edyta; Brzosko, Szymon; Malyszko, Jacek; Mysliwiec, Michal
CORPORATE SOURCE: Department of Nephrology and Internal Medicine, Bialystok School of Medicine, Zurawia 14, PL-15-540, Bialystok, Poland
SOURCE: Nephron, (March, 2002) Vol. 90, No. 3, pp. 282-289. print.
CODEN: NPRNAY. ISSN: 0028-2766.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Apr 2002
Last Updated on STN: 24 Apr 2002
AB Insulin-like growth factor (IGF) system components appear to be the most important regulators of bone cell function. On the other hand, **IGF-1** is shown to be an important regulator for

erythropoiesis. The aim of the study was to examine the relationships between IGF system, requirements of erythropoietin, endogeneous erythropoietin levels, bone metabolism assesed by biochemical markers, markers of nutrition such as cholesterol and albumin in recombinant **human** erythropoietin (rHuEPO)-treated patients maintained on chronic hemodialyses or peritoneal dialyses as well as in kidney transplant recipients. The studies were performed on 79 chronically hemodialyzed patients; 28 of them did not receive rHuEPO, 51 subjects received rHuEPO, 34 patients on continuous ambulatory peritoneal dialysis (CAPD), 16 of them did not receive rHuEPO, 18 were given rHuEPO and 46 kidney allograft recipients. Endogeneous erythropoietin concentration, bone-specific alkaline phosphatase and serum CrossLaps were assayed by ELISA. Intact PTH, osteocalcin, 1,25-(OH)2 D3, 25-OH D3, **IGF-1**, procollagen type I carboxy-terminal extension peptide (PICP) and procollagen type I cross-linked carboxy-terminal telopeptide (ICTP) were studied by RIA, whereas IGFBP-1 and IGFBP-3 concentrations were assayed by IRMA. We found a significantly higher **IGF-1** and IGFBP-3 in rHuEPO-treated HD patients when compared to CAPD subjects given rHuEPO as well as to hemodialysis (HD) patients not treated with rHuEPO. **IGF-1** was significantly higher in kidney transplant recipients when compared to dialyzed patients without rHuEPO therapy. IGFBP-1 was similar in all groups of patients (including kidney transplant recipients) studied. In CAPD patients not given rHuEPO concentrations of ICTP and PICP were significantly lower when compared to rHuEPO-treated CAPD subjects and HD patients not receiving rHuEPO therapy. Serum CrossLaps in CAPD patients treated with rHuEPO were significantly higher when compared to CAPD subjects without rHuEPO treatment and to kidney transplant recipients. In rHuEPO-treated CAPD subjects **IGF-1** and IGFBP-1 correlated positively with serum CrossLaps ($r=0.61$, $p<0.05$ and $r=0.64$, $p<0.05$, respectively), whereas in hemodialyzed patients without rHuEPO a significant negative correlation between IGFBP-3 and serum CrossLaps was found ($r=-0.69$, $p<0.001$) as well as between IGFBP-3 and aluminium ($r=0.51$, $p<0.05$), **IGF-1** and ICTP ($r=-0.43$, $p<0.05$). In conclusion, our data indicate a probable functional relationship between IGF system components, erythropoietin treatment in dialyzed patients and bone metabolism in renal replacement therapy in a form of hemodialyses, peritoneal dialyses and kidney transplantation. Dialyzed patients exhibit more pronounced renal osteodystrophy than kidney allograft recipients. IGF system components are influenced by erythropoietin therapy, but are not related to serum erythropoietin levels and rHuEPO requirements.

L8 ANSWER 12 OF 41 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 2002044228 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11771659
TITLE: Large-scale screening for candidate genes of ossification of the posterior longitudinal ligament of the spine.
AUTHOR: Furushima Kozo; Shimo-Onoda Kazuki; Maeda Shingo; Nobukuni Takahiro; Ikari Katsunori; Koga Hiroaki; Komiya Setsuro; Nakajima Toshiaki; Harata Seiko; Inoue Ituro
CORPORATE SOURCE: Division of Genetic Diagnosis, The Institute of Medical Science. The University of Tokyo, Japan.
SOURCE: Journal of bone and mineral research : official journal of the American Society for Bone and Mineral Research, (2002 Jan) 17 (1) 128-37.
Journal code: 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020124
Last Updated on STN: 20020618
Entered Medline: 20020617

AB Ossification of the posterior longitudinal ligament of the spine (OPLL) is the predominant myelopathy among Japanese, and is usually diagnosed by ectopic bone formation in the paravertebral ligament in Japanese and other Asians. To detect genetic determinants associated with OPLL, we performed an extensive nonparametric linkage study with 126 affected sib-pairs using markers for various candidate genes by distinct analyses, SIBPAL and GENEHUNTER. Eighty-eight candidate genes were selected by comparing the

genes identified by complementary DNA (cDNA) microarray analysis of systematic gene expression profiles during osteoblastic differentiation of **human** mesenchymal stem cells with the genes known to be involved in bone metabolism. Of the 24 genes regulated during osteoblastic differentiation, only one, the alpha B **crystalline** gene, showed evidence of linkage ($p = 0.016$, nonparametric linkage [NPL] score = 1.83). Of 64 genes known to be associated with bone metabolism, 7 showed weak evidence of linkage by SIBPAL analysis ($p < 0.05$): cadherin 13 (CDH13), bone morphogenetic protein 4 (BMP4), proteoglycan 1 (PRG1), transforming growth factor beta 3 (TGFb3), osteopontin (OPN), parathyroid hormone receptor 1 (PTHR1), and **insulin-like growth factor 1** (IGF1). Among these genes, BMP4 (NPL = 2.23), CDH13 (NPL = 2.00), TGFb3 (NPL = 1.30), OPN (NPL = 1.15), and PTHR1 (NPL = 1.00) showed evidence of linkage by GENEHUNTER. Only BMP4 reached criteria of suggestive evidence of linkage. Because this gene is a well-known factor in osteogenetic function, BMP4 should be screened in further study for the polymorphism responsible.

L8 ANSWER 13 OF 41 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2002:607872 SCISEARCH
THE GENUINE ARTICLE: 574GF
TITLE: The chitinase 3-like protein **human** cartilage glycoprotein 39 (HC-gp39) stimulates proliferation of **human** connective-tissue cells and activates both extracellular signal-regulated kinase- and protein kinase beta-mediated signalling pathways
AUTHOR: Recklies A D (Reprint); White C; Ling H
CORPORATE SOURCE: Shriners Hosp Children, Joint Dis Lab, 1529 Cedar Ave, Montreal, PQ H3G 1A6, Canada (Reprint); Shriners Hosp Children, Joint Dis Lab, Montreal, PQ H3G 1A6, Canada; McGill Univ, Dept Surg, Montreal, PQ H3G 1Y6, Canada
COUNTRY OF AUTHOR: Canada
SOURCE: BIOCHEMICAL JOURNAL, (1 JUL 2002) Vol. 365, Part 1, pp. 119-126.
Publisher: PORTLAND PRESS, 59 PORTLAND PLACE, LONDON W1N 3AJ, ENGLAND.
ISSN: 0264-6021.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 47
*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB **Human** cartilage glycoprotein 39 (HC-gp39) is a glycoprotein secreted by articular chondrocytes, synoviocytes and macrophages. Increased levels of HC-gp39 have been demonstrated in synovial fluids of patients with rheumatoid or osteoarthritis. The increased secretion of HC-gp39 under physiological and pathological conditions with elevated connective-tissue turnover suggests its involvement in the homoeostasis of these tissues. We report here that HC-gp39 promotes the growth of **human** synovial cells as well as skin and fetal lung fibroblasts. A dose-dependent growth stimulation was observed when each of the fibroblastic cell lines was exposed to HC-gp39 in a concentration range from 0.1 to 2 nM, which is similar to the effective dose of the well-characterized mitogen, **insulin-like growth factor-1**, At suboptimal concentrations, the two growth factors work in a synergistic fashion. The use of selective inhibitors of the mitogen-activated protein kinase and the protein kinase B (AKT) signalling pathways indicates that both are involved in mediating the mitogenic response to HC-gp39. Phosphorylation of both extracellular signal-regulated kinases 1/2 and AKT occurred in a dose- and time-dependent fashion upon addition of HC-gp39. Activation of these signalling pathways could also be demonstrated in **human** chondrocytes. Thus HC-gp39 initiates a signalling cascade in connective-tissue cells which leads to increased cell proliferation, suggesting that this protein could play a major role in the pathological conditions leading to tissue fibrosis.

L8 ANSWER 14 OF 41 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2001502871 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11551198
TITLE: **Crystal** structure of **human** **insulin-like growth**

**factor-1**: detergent binding inhibits
binding protein interactions.
AUTHOR: Vajdos F F; Ultsch M; Schaffer M L; Deshayes K D; Liu J; Skelton N J; de Vos A M
CORPORATE SOURCE: Department of Protein Engineering, Genentech, Inc., 1 DNA Way, South San Francisco, California 94080, USA.
SOURCE: Biochemistry, (2001 Sep 18) 40 (37) 11022-9.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1IMX
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010913
Last Updated on STN: 20011022
Entered Medline: 20011018

AB Despite efforts spanning considerably more than a decade, a high-resolution view of the family of proteins known as insulin-like growth factors (IGFs) has remained elusive. **IGF-1** consists of three helical segments which are connected by a 12-residue linker known as the C-region. NMR studies of members of this family reveal a dynamic structure with a topology resembling insulin but little structural definition in the C-region. We have **crystallized** **IGF-1** in the presence of the detergent deoxy big CHAPS, and determined its structure at 1.8 A resolution by multiwavelength anomalous diffraction, exploiting the anomalous scattering of a single bromide ion and six of the seven sulfur atoms of **IGF-1** . The structure reveals a well-defined conformation for much of the C-region, which extends away from the core of **IGF-1** and has residues known to be involved in receptor binding prominently displayed in a type II beta-turn. In the **crystal**, these residues form a dimer interface, but analytical ultracentrifugation experiments demonstrate that at physiological concentrations **IGF -1** is monomeric. A single detergent molecule contacts residues known to be important for **IGF-1** binding protein (IGFBP) interactions. Biophysical and biochemical data show that the detergent binds to **IGF-1** specifically and blocks binding of IGFBP-1 and IGFBP-3.

L8 ANSWER 15 OF 41 MEDLINE on STN
ACCESSION NUMBER: 2001406019 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11456486
TITLE: Structure-function analysis of a phage display-derived peptide that binds to insulin-like growth factor binding protein 1.
AUTHOR: Skelton N J; Chen Y M; Dubree N; Quan C; Jackson D Y; Cochran A; Zobel K; Deshayes K; Baca M; Pisabarro M T; Lowman H B
CORPORATE SOURCE: Department of Protein Engineering, Genentech, Inc., 1 DNA Way, South San Francisco, California 94080, USA.. skelly@gene.com
SOURCE: Biochemistry, (2001 Jul 24) 40 (29) 8487-98.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1GJE; PDB-1GJG; PDB-1IGF; PDB-1IMW; PDB-1IN2; PDB-1IN3
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20011008
Last Updated on STN: 20011008
Entered Medline: 20011004

AB Highly structured, peptide antagonists of the interaction between **insulin-like growth factor 1** (IGF-I) and IGF binding protein 1 (IGFBP-1) have recently been discovered by phage display of naive peptide libraries [Lowman, H. B., et al. (1998) Biochemistry 37, 8870--8878]. We now report a detailed analysis of the features of this turn-helix peptide motif that are necessary for IGFBP-1 binding and structural integrity. Further rounds of phage randomization indicate the importance of residues contributing to a hydrophobic patch on

one face of the helix. Alanine-scanning substitutions confirm that the hydrophobic residues are necessary for binding. However, structural analysis by NMR spectroscopy indicates that some of these analogues are less well folded. Structured, high-affinity analogues that lack the disulfide bond were prepared by introducing a covalent constraint between side chains at positions i and i + 7 or i + 8 within the helix. Analogues based on this scaffold demonstrate that a helical conformation is present in the bound state, and that hydrophobic side chains in this helix, and residues immediately preceding it, interact with IGFBP-1. By comparison of alanine scanning data for IGF-I and the turn-helix peptide, we propose a model for common surface features of these molecules that recognize IGFBP-1.

L8 ANSWER 16 OF 41 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:775999 CAPLUS
DOCUMENT NUMBER: 136:64596
TITLE: Insulin and **IGF-1** induce different patterns of gene expression in mouse fibroblast NIH-3T3 cells: identification by cDNA microarray analysis
AUTHOR(S): Dupont, Joelle; Khan, Javed; Qu, Bao-He; Metzler, Paul; Helman, Lee; LeRoith, Derek
CORPORATE SOURCE: Section on Cellular and Molecular Physiology, Clinical Endocrinology Branch, National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, MD, 20892-1758, USA
SOURCE: Endocrinology (2001), 142(11), 4969-4975
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **IGF-1** receptor and the related insulin receptor are similar in structure and activate many of the same postreceptor signaling pathways, yet they mediate distinct biol. functions. It is still not understood how the specificity of insulin vs. **IGF-1** signaling is controlled. In this study, the authors have used cDNA microarrays to monitor the gene expression patterns that are regulated by insulin and **IGF-1**. Mouse fibroblast NIH-3T3 cells expressing either the wild-type **human** IGF receptor or the insulin receptor were stimulated with either **IGF-1** or insulin, resp. Thirty genes, 27 of which were not previously known to be **IGF-1** responsive, were up-regulated by **IGF-1** but not by insulin. Nine genes, none of which was previously known to be insulin responsive, were up-regulated by insulin but not by **IGF-1**. The IGF- and insulin-induced regulation of 10 of these genes was confirmed by Northern blot anal. Interestingly, more than half of the genes up-regulated by **IGF-1** are assocd. with mitogenesis and differentiation, whereas none of the genes specifically up-regulated by insulin are assocd. with these processes. The authors' results indicate that under the conditions used in this study, **IGF-1** is a more potent activator of the mitogenic pathway than insulin in mouse fibroblast NIH-3T3 cells.
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 17 OF 41 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2001677321 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11694888
TITLE: Structure and autoregulation of the **insulin-like growth factor 1** receptor kinase.
AUTHOR: Favelyukis S; Till J H; Hubbard S R; Miller W T
CORPORATE SOURCE: Department of Physiology and Biophysics, School of Medicine State University of New York at Stony Brook, Stony Brook, New York 11794, USA.
SOURCE: Nature structural biology, (2001 Dec) 8 (12) 1058-63.
Journal code: 9421566. ISSN: 1072-8368.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

OTHER SOURCE: PDB-1K3A
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011128
Last Updated on STN: 20020124
Entered Medline: 20020102

AB The **insulin-like growth factor 1** (IGF1) receptor is closely related to the insulin receptor. However, the unique biological functions of IGF1 receptor make it a target for therapeutic intervention in **human** cancer. Using its isolated tyrosine kinase domain, we show that the IGF1 receptor is regulated by intermolecular autophosphorylation at three sites within the kinase activation loop. Steady-state kinetic analyses of the isolated phosphorylated forms of the IGF1 receptor kinase (IGF1RK) reveal that each autophosphorylation event increases enzyme turnover number and decreases Km for ATP and peptide. We have determined the 2.1 A-resolution **crystal** structure of the tris-phosphorylated form of IGF1RK in complex with an ATP analog and a specific peptide substrate. The structure of IGF1RK reveals how the enzyme recognizes peptides containing hydrophobic residues at the P+1 and P+3 positions and how autophosphorylation stabilizes the activation loop in a conformation that facilitates catalysis. Although the nucleotide binding cleft is conserved between IGF1RK and the insulin receptor kinase, sequence differences in the nearby interlobe linker could potentially be exploited for anticancer drug design.

L8 ANSWER 18 OF 41 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2001544932 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11591350
TITLE: **Crystal** structure of bisphosphorylated **IGF-1** receptor kinase: insight into domain movements upon kinase activation.
AUTHOR: Pautsch A; Zoephel A; Ahorn H; Spevak W; Hauptmann R; Nar H
CORPORATE SOURCE: Boehringer Ingelheim Pharma KG Deutschland, Birkendorferstrasse 65, D-88400 Biberach, Germany.. alexander.pautsch@bc.boehringer-ingelheim.com
SOURCE: Structure (Cambridge, Mass. : 2001), (2001 Oct) 9 (10) 955-65.
Journal code: 101087697. ISSN: 0969-2126.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1JQH
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011010
Last Updated on STN: 20020125
Entered Medline: 20020115

AB BACKGROUND: The **insulin-like growth-factor-1** (**IGF-1**) receptor, which is widely expressed in cells that have undergone oncogenic transformation, is emerging as a novel target in cancer therapy. **IGF-1** -induced receptor activation results in autophosphorylation of cytoplasmic kinase domains and enhances their capability to phosphorylate downstream substrates. Structures of the homologous insulin receptor kinase (IRK) exist in an open, unphosphorylated form and a closed, trisphosphorylated form. RESULTS: We have determined the 2.1 A **crystal** structure of the **IGF-1** receptor protein tyrosine kinase domain phosphorylated at two tyrosine residues within the activation loop (IGF-1RK2P) and bound to an ATP analog. The ligand is not in a conformation compatible with phosphoryl transfer, and the activation loop is partially disordered. Compared to the homologous insulin receptor kinase, IGF-1RK2P is trapped in a half-closed, previously unobserved conformation. Observed domain movements can be dissected into two orthogonal rotational components. CONCLUSIONS: Conformational changes upon kinase activation are triggered by the degree of phosphorylation and are crucially dependent on the conformation of the proximal end of the kinase activation loop. This IGF-1RK structure will provide a molecular basis for the design of selective antioncogenic therapeutic agents.

L8 ANSWER 19 OF 41 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2001:791570 SCISEARCH

THE GENUINE ARTICLE: 477LJ
TITLE: Monitoring the activation state of the insulin receptor using bioluminescence resonance energy transfer
AUTHOR: Boute N; Pernet K; Issad T (Reprint)
CORPORATE SOURCE: Inst Cochin Genet Mol, CNRS, UPR 415, 22 Rue Mechain, F-75014 Paris, France (Reprint); Inst Cochin Genet Mol, CNRS, UPR 415, F-75014 Paris, France
COUNTRY OF AUTHOR: France
SOURCE: MOLECULAR PHARMACOLOGY, (OCT 2001) Vol. 60, No. 4, pp. 640-645.
Publisher: AMER SOC PHARMACOLOGY EXPERIMENTAL THERAPEUTICS 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA.
ISSN: 0026-895X.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 17

*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB We have developed a procedure based on bioluminescence resonance energy transfer (BRET) to monitor the activation state of the insulin receptor in vitro. **Human** insulin receptor cDNA was fused to either Renilla luciferase (Rluc) or enhanced yellow fluorescent protein (EYFP) coding sequences. Fusion insulin receptors were partially purified by wheat-germ lectin chromatography from **human** embryonic kidney 293 cells cotransfected with these constructs. The conformational change induced by insulin on its receptor could be detected as an energy transfer (BRET signal) between Rluc and EYFP. BRET signal parallels insulin-induced autophosphorylation of the fusion receptor. Dose-dependent effects of **insulin, insulin-like growth factor 1**, and epidermal growth factor on BRET signal are in agreement with known pharmacological properties of these ligands. Moreover, antibodies that activate or inhibit the auto phosphorylation of the receptor have similar effects on BRET signal. This method allows for rapid analysis of the effects of agonists on insulin receptor activity and could therefore be used in a high-throughput screening test for discovery of molecules with insulin-like properties.

L8 ANSWER 20 OF 41 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:320469 BIOSIS
DOCUMENT NUMBER: PREV200200320469
TITLE: Renal contraction therapy for enlarged polycystic kidneys by transcatheter arterial embolization.
AUTHOR(S): Ubara, Yoshifumi [Reprint author]; Tagami, T. [Reprint author]; Katori, H. [Reprint author]; Yokota, M. [Reprint author]; Takemoto, F. [Reprint author]; Inoue, S. [Reprint author]; Kuzuhara, K. [Reprint author]; Hara, S. [Reprint author]; Yamada, A. [Reprint author]
CORPORATE SOURCE: Kidney Center, Toranomon Hospital, Tokyo, Japan
SOURCE: Journal of the American Society of Nephrology, (September, 2001) Vol. 12, No. Program and Abstract Issue, pp. 546A. print.
Meeting Info.: ASN (American Society of Nephrology)/ISN (International Society of Nephrology) World Congress of Nephrology. San Francisco, CA, USA. October 10-17, 2001.
CODEN: JASNEU. ISSN: 1046-6673.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Jun 2002
Last Updated on STN: 5 Jun 2002

L8 ANSWER 21 OF 41 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2001341410 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11336503
TITLE: FGF signaling in chick lens development.
AUTHOR: Le A C; Musil L S
CORPORATE SOURCE: Vollum Institute for Advanced Biomedical Research, Oregon Health Sciences University, Portland, Oregon 97201, USA.
CONTRACT NUMBER: EY11117 (NEI)
SOURCE: Developmental biology, (2001 May 15) 233 (2) 394-411.
Journal code: 0372762. ISSN: 0012-1606.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010618
Last Updated on STN: 20010618
Entered Medline: 20010614

AB The prevailing concept has been that an FGF induces epithelial-to-fiber differentiation in the mammalian lens, whereas chick lens cells are unresponsive to FGF and are instead induced to differentiate by IGF/insulin-type factors. We show here that when treated for periods in excess of those used in previous investigations (>5 h), purified recombinant FGFs stimulate proliferation of primary cultures of embryonic chick lens epithelial cells and (at higher concentrations) expression of the fiber differentiation markers delta-**crystallin** and CP49. Surprisingly, upregulation of proliferation and delta-**crystallin** synthesis by FGF does not require activation of ERK kinases. ERK function is, however, essential for stimulation of delta-**crystallin** expression in response to insulin or **IGF-1**. Vitreous humor, the presumptive source of differentiation-promoting activity in vivo, contains a factor capable of diffusing out of the vitreous body and inducing delta-**crystallin** and CP49 expression in chick lens cultures. This factor binds heparin with high affinity and increases delta-**crystallin** expression in an ERK-insensitive manner, properties consistent with an FGF but not insulin or IGF. Our findings indicate that differentiation in the chick lens is likely to be mediated by an FGF and provide the first insights into the role of the ERK pathway in growth factor-induced signal transduction in the lens.


L8 ANSWER 22 OF 41 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2002018312 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11441649
TITLE: Relationship between circulating levels of sex hormones and **insulin-like growth factor-1** and fluid intelligence in older men.
AUTHOR: Aleman A; de Vries W R; Koppeschaar H P; Osman-Dualeh M; Verhaar H J; Samson M M; Bol E; de Haan E H
CORPORATE SOURCE: Department of Endocrinology, University Hospital Utrecht, The. Netherlands.A.Aleman@fss.uu.nl
SOURCE: Experimental aging research, (2001 Jul-Sep) 27 (3) 283-91. Journal code: 7603335. ISSN: 0361-073X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20020121
Last Updated on STN: 20020121
Entered Medline: 20011207

AB The relationship was investigated between baseline serum levels of total testosterone (T), free testosterone (FT), dehydroepiandrosterone sulfate (DHEAS), ESTRADIOL (E2), sex hormone-binding globulin (SHBG), **insulin-like growth factor-1** (**IGF-1**) and cognitive functioning in 25 healthy older men (mean age 69.1 years). Cognitive tests concerned measures not sensitive to ageing (**crystallized** intelligence), and measures sensitive to ageing (fluid intelligence and verbal long-term memory). Partial correlation coefficients (controlled for level of education) revealed significant associations of total T (r = -.52, p = -.009), SHBG (r - .59, p = .002) and **IGF-1** (r = .54, p = .007) with the composite measure of fluid intelligence test performance, but not with **crystallized** intelligence, nor verbal long-term memory. Stepwise hierarchical regression analysis with the composite measure of fluid intelligence as the dependent variable showed that the contributions of SHBG, total T, and **IGF-1** were not additive.

L8 ANSWER 23 OF 41 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:299375 BIOSIS

DOCUMENT NUMBER: PREV200200299375
TITLE: Hyperleptinemia is mediated by insulin but not by renal function in pre-dialysis and kidney transplant patients.
AUTHOR(S): Fouque, Denis [Reprint author]; Geelen, Ghislaine; Bernhard, Jacques [Reprint author]; Joly, Marie-Odile [Reprint author]; Hadj-Aissa, Aoumeur; Allevard, Anne-Marie; Laville, Maurice [Reprint author]
CORPORATE SOURCE: Nephrology, Hosp E. Herriot, Lyon, France
SOURCE: Journal of the American Society of Nephrology, (September, 2001) Vol. 12, No. Program and Abstract Issue, pp. 202A. print.
Meeting Info.: ASN (American Society of Nephrology)/ISN (International Society of Nephrology) World Congress of Nephrology. San Francisco, CA, USA. October 10-17, 2001. American Society of Nephrology; International Society of Nephrology.
CODEN: JASNEU. ISSN: 1046-6673.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 22 May 2002
Last Updated on STN: 22 May 2002

L8 ANSWER 24 OF 41 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 2002391114 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12138993
TITLE: Sarcoidosis within a pituitary adenoma.
AUTHOR: Rubin M R; Bruce J N; Khandji A G; Freda P U
CORPORATE SOURCE: Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA.
SOURCE: Pituitary, (2001 Aug) 4 (3) 195-202.
Journal code: 9814578. ISSN: 1386-341X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020726
Last Updated on STN: 20020813
Entered Medline: 20020812

AB A 54 year old man presented with frontal headaches for one year. A CT scan of the head revealed a pituitary mass. He denied a change in vision or galactorrhea, but did have decreased frequency of erections and a recent episode of renal stones. On physical exam, the cranial nerves were normal. Visual field exam revealed mild bilateral temporal defects. The genitalia were normal and the testes were soft. Laboratory evaluation revealed: Na, 134 mM/l; K, 6.7 mM/l; Cl, 104 mM/l; HCO3, 22 mM/l; BUN, 47 mg/dl; Cr, 8.3 mg/dl; Ca, 12.5 mg/dl; Phos, 5.5 mg/dl; prolactin, 32.0 ng/ml; T4, 4.46 microg/dl; TSH, 2.07 microU/ml; LH, 18.1 mIU/ml; FSH 3.2 mIU/ml; alpha subunit 1.6 ng/ml; testosterone 255 ng/dl; cortisol, 20.3 microg/dl; cortisol after 250 microg cortrosyn, 38.5 microg/dl (time 60 minutes); growth hormone, 1.4 ng/ml; **IGF-1**, 47 ng/ml; PTH, <1 pg/ml; 25-hydroxyvitamin D, 14 ng/ml; 1,25-dihydroxyvitamin D, 69 pg/ml. These results were felt to be consistent with a non-PTH-mediated hypercalcemia, such as humoral hypercalcemia of malignancy, or a vitamin D-mediated hypercalcemia, such as lymphoma, sarcoidosis or tuberculosis. Head MRI demonstrated a 3.5 x 3.5 x 2.5 cm heterogeneous mass enlarging the sella, deforming the clivus and compressing the cavernous sinus, basilar artery and left side of the optic chiasm. There was a small focus of high signal in the superior part of the mass on the T1-weighted image from either a proteinaceous cyst with early calcium deposition or sub-acute blood. These radiographic findings were felt to be consistent with a pituitary adenoma. The patient was treated with intravenous hydration and thyroxine 50 microg daily and underwent a transsphenoidal resection of the pituitary lesion. Pathologic examination revealed a pituitary adenoma with multiple granulomas and **crystalline** material; this was consistent with sarcoid within the adenoma. Post-operatively, the serum LH fell to 5.5 mIU/ml. A subsequent transbronchial biopsy revealed multiple non-caseating granulomas. A serum

ACE level was elevated at 132.6 U/l. He received oral prednisone 60 mg daily with resolution of the hypercalcemia. Neurosarcoidosis occurs in 5 to 15% of patients with sarcoidosis and can involve the hypothalamus and pituitary gland. This is the first reported case of sarcoidosis occurring within a pituitary adenoma.

L8 ANSWER 25 OF 41 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:487665 CAPLUS
DOCUMENT NUMBER: 136:146715
TITLE: Molecular Cloning, Developmental Expression, and Hormonal Regulation of Zebrafish (Danio rerio) .beta. **Crystallin** B1, a Member of the Superfamily of .beta. **Crystallin** Proteins
AUTHOR(S): Chen, Jyh-Yih; Chang, Bei-En; Chen, Yi-Hsuan; Lin, Cliff Ji-Fan; Wu, Jen-Leih; Kuo, Ching-Ming
CORPORATE SOURCE: Institute of Zoology, Academia Sinica, Nankang, Taipei, Taiwan
SOURCE: Biochemical and Biophysical Research Communications (2001), 285(1), 105-110
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cDNA sequence of .beta. **crystallin** B1 was detd. from zebrafish (Danio rerio) and compared to the corresponding genes of bovine, rat, chicken, **human**, and Xenopus. Multispecies comparison of superfamily diversity demonstrated .beta. **crystallin** B1 homol. between zebrafish, bovine, chicken, and rat, but large distances to .beta. **crystallin** B2 and B3. Zebrafish cDNA has a size of 943 nucleotides and encodes a polypeptide of 233 amino acids. Zebrafish .beta. **crystallin** B1 shares 71.30, 75.86, and 71.00% similarities with bovine, chicken, and rat .beta. **crystallin** B1, resp. Northern blot anal. revealed a single 0.9-kb .beta. **crystallin** B1 transcript which was expressed and progressively increased in the first 20 h of zebrafish embryogenesis. Whole-mount in situ hybridization revealed that the .beta. **crystallin** B1 transcript was only specifically expressed in the lens region of the eye. A starvation expt. revealed no variation in mRNA levels after 14 and 21 days. An expt. in which hormone was injected showed that the .beta. **crystallin** B1 transcript first increased 24 h after the injection of insulin-like growth factor I, insulin-like growth factor II, or growth hormone, then decreased 48 h after injection. The .beta. **crystallin** B1 transcript continuously increased after insulin was injected. Taken together, our results identify the early specific expression of .beta. **crystallin** B1 within the lens. Despite small differences, these results indicate that both the structure of the .beta. **crystallin** B1 protein and its involvement with regulation by growth factors appear to have been remarkably conserved. (c) 2001 Academic Press.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 26 OF 41 MEDLINE on STN
ACCESSION NUMBER: 2001292403 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11374867
TITLE: Downregulated expression of integrin alpha6 by transforming growth factor-beta(1) on lens epithelial cells in vitro.
AUTHOR: Lim J M; Kim J A; Lee J H; Joo C K
CORPORATE SOURCE: Department of Ophthalmology and Visual Science, College of Medicine, Catholic University of Korea, and Catholic Research Institutes of Medical Sciences, Seoul, Korea.
SOURCE: Biochemical and biophysical research communications, (2001 Jun 1) 284 (1) 33-41.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723

Entered Medline: 20010719

AB Integrins represent the main cell surface receptors that mediate cell-matrix and cell-cell interactions. They play critical roles in adhesion, migration, morphogenesis, and the differentiation of several cell types. Previous studies have demonstrated that members of the fibroblast growth factor (FGF)-2, transforming growth factor (TGF)-beta(1), and insulin growth factor (**IGF**)-**1** play important roles in lens biology. In particularly, TGF-beta(1) appears to play a key role in extracellular matrix production, cell proliferation, and cell differentiation of lens epithelial cells. In this study we investigated the effects of FGF-2, TGF-beta(1), and **IGF-1** on the modulation of integrin receptors using lens epithelial cell lines (HLE B-3 and alphaTN-4) and lens explants. We found that the expression of integrin alpha6 is downregulated by TGF-beta(1), but is not responsive to FGF-2 or **IGF-1**. The promoter activity of the integrin alpha6 gene decreased upon TGF-beta(1) treatment in a transient transfection assay, and flow cytometric analysis demonstrated the reduced expression of integrin alpha6 by TGF-beta(1), whereas significant changes were not observed in the level of integrin alpha6 after the addition of FGF-2. These findings suggest that the reduced expression of integrin alpha6 caused by TGF-beta(1) might play a role in the activation of the cell cycle genes required during the fiber differentiation of the lens.



L8 ANSWER 27 OF 41 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

ACCESSION NUMBER: 2001:918 SCISEARCH
THE GENUINE ARTICLE: 383ET
TITLE: Expression of cartilage intermediate layer protein/nucleotide pyrophosphohydrolase parallels the production of extracellular inorganic pyrophosphate in response to growth factors and with aging
AUTHOR: Hirose J (Reprint); Masuda I; Ryan L M
CORPORATE SOURCE: Med Coll Wisconsin, Dept Med, Div Rheumatol, 9200 W Wisconsin Ave, Milwaukee, WI 53226 USA (Reprint); Med Coll Wisconsin, Dept Med, Div Rheumatol, Milwaukee, WI 53226 USA
COUNTRY OF AUTHOR: USA
SOURCE: ARTHRITIS AND RHEUMATISM, (DEC 2000) Vol. 43, No. 12, pp. 2703-2711.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
ISSN: 0004-3591.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 55

*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Objective, To evaluate the role of the extracellular inorganic pyrophosphate (ePPi)-generating ectoenzyme cartilage intermediate layer protein/nucleotide pyrophosphohydrolase (CILP/NTPPH) in chondrocyte PPI elaboration, we studied CILP/NTPPH expression in response to growth factors during aging.

Methods. Porcine chondrocytes from adult (3-4-year-old) and young (2-week-old) animals were stimulated with transforming growth factor beta1 (TGF beta1), which enhances ePPi elaboration, and/or **insulin-like growth factor 1** (**IGF-1**), which diminishes ePPi elaboration. Measurements of ePPi, NTPPH enzyme activity, Western blot analysis, reverse transcriptase-polymerase chain reaction (RT-PCR), and Northern blot analysis were performed.

Results. Elaboration of ePPi into conditioned media from adult chondrocytes was significantly increased by TGF beta1 and significantly inhibited by **IGF-1**, but no significant differences were observed in young chondrocytes. The protein levels of CILP/NTPPH by Western analysis in the media from adult and young porcine chondrocytes were increased by TGF beta1, RT-PCR and Northern analysis showed that CILP/NTPPH messenger RNA (mRNA) expression in both adult and young chondrocytes was increased by TGF beta1 and decreased by **IGF-1**, but these changes were less significant in the young chondrocytes, Basal and TGF beta1-upregulated levels of CILP/NTPPH expression were higher in adult chondrocytes than in young chondrocytes,

Conclusion. These results provide evidence that CILP/NTPPH expression

and ePPi elaboration are concomitantly stimulated by TGF beta1 and down-regulated by **IGF-1**, especially in adult chondrocytes, implicating CILP/NTPPH as a functional participant in ePPi elaboration. Increased CILP/NTPPH mRNA expression in chondrocytes derived from aged animals compared with young animals might promote the formation of calcium pyrophosphate dihydrate **crystals** in aged cartilage.

L8 ANSWER 28 OF 41 MEDLINE on STN
ACCESSION NUMBER: 2000453442 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11011693
TITLE: Ex vivo canine lens capsular sac explants.
AUTHOR: Davidson M G; Wormstone M; Morgan D; Malakof R; Allen J; McGahan M C
CORPORATE SOURCE: College of Veterinary Medicine, North Carolina State University, Raleigh 27606, USA.. mike_davidson@ncsu.edu
CONTRACT NUMBER: EY04900 (NEI)
SOURCE: Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie, (2000 Aug) 238 (8) 708-14.
Journal code: 8205248. ISSN: 0721-832X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010125

AB BACKGROUND: Lens capsular sac explants from **human** cadaver eyes were used to investigate posterior capsular opacification (PCO). The purpose of this study was to characterize a similar model using canine tissue and to determine whether transferrin (Tf), transforming growth factor beta-2 (TGF-beta2), and **insulin-like growth factor-1** (**IGF-1**) are secreted by lens epithelial cells (LEC) of these ex vivo sacs. METHODS: The lens from canine eyes was removed by extracapsular cataract extraction, the lens sac dissected free, pinned to a petri dish, and cultured in either serum-supplemented or serum-free medium. Morphologic characteristics and growth rate to confluence on the posterior capsule were studied by phase-contrast microscopy. Vimentin, alpha smooth muscle actin, and panTGF-beta expression by LEC were determined by immunohistochemistry. Tf, TGF-beta2, and **IGF-1** levels were measured by ELISA in the supernatant of sacs cultured in serum-free medium. RESULTS: The mean time to confluence of LEC onto the posterior capsule was 5.4+/-1.1 days (n=22) and 14.7+/-3.7 days (n=14) for sacs in serum-supplemented and serum-free medium, respectively. Following development of confluence, explants displayed opacification and light scatter from cellular proliferation and capsular contraction. Confluent LEC expressed vimentin, alpha smooth muscle actin, and TGF-beta2, and both Tf and TGF-beta2 were secreted into the culture supernatant. CONCLUSION: Canine lens sac explants have characteristics virtually identical to those of **human** origin, and appear to be a useful alternative tissue source for this model when **human** cadaver eyes are unavailable. Tf and TGFbeta-2, but not **IGF-1**, are secreted by LEC in explanted lens sacs and may influence the proliferation and metaplasia of LEC during the development of PCO.

L8 ANSWER 29 OF 41 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2000:183630 SCISEARCH
THE GENUINE ARTICLE: 288VT
TITLE: Characterization of a comparative model of the extracellular domain of the epidermal growth factor receptor
AUTHOR: Jorissen R N (Reprint); Epa V C; Treutlein H R; Garrett T P J; Ward C W; Burgess A W
CORPORATE SOURCE: ROYAL MELBOURNE HOSP, LUDWIG INST CANC RES, POB 2008, PARKVILLE, VIC 3050, AUSTRALIA (Reprint); BIOMOL RES INST, PARKVILLE, VIC 3052, AUSTRALIA; COMMONWEALTH SCI & IND RES ORG, DIV HLTH SCI & NUTR, PARKVILLE, VIC 3052, AUSTRALIA; ROYAL MELBOURNE HOSP, COOPERAT RES CTR CELLULAR GROWTH

FACTORS, PARKVILLE, VIC 3050, AUSTRALIA
COUNTRY OF AUTHOR: AUSTRALIA
SOURCE: PROTEIN SCIENCE, (FEB 2000) Vol. 9, No. 2, pp. 310-324. Publisher: CAMBRIDGE UNIV PRESS, 40 WEST 20TH STREET, NEW YORK, NY 10011-4211. ISSN: 0961-8368.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 78

*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB The Epidermal Growth Factor (EGF) receptor is a tyrosine kinase that mediates the biological effects of ligands such as EGF and transforming growth factor alpha. An understanding of the molecular basis of its action has been hindered by a lack of structural and mutational data on the receptor. We have constructed comparative models of the four extracellular domains of the EGF receptor that are based on the structure of the first three domains of the **insulin-like growth factor-1** (**IGF-1**) receptor. The first and third domains of the EGF receptor, L1 and L2, are right-handed beta helices. The second and fourth domains of the EGF receptor, S1 and S2, consist of the modules held together by disulfide bonds, which, except for the first module of the Si domain, form rod-like structures. The arrangement of the LI and S1 domains of the model are similar to that of the first two domains of the **IGF-1** receptor, whereas that of the L2 and S2 domains appear to be significantly different. Using the EGF receptor model and limited information from the literature, we have proposed a number of regions that may be involved in the functioning of the receptor. In particular, the faces containing the large beta sheets in the L1 and L2 domains have been suggested to be involved with ligand binding of EGF to its receptor.

L8 ANSWER 30 OF 41 MEDLINE on STN
ACCESSION NUMBER: 2001018198 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11023783
TITLE: Ligand-induced conformational change in the minimized insulin receptor.
AUTHOR: Schlein M; Havelund S; Kristensen C; Dunn M F; Kaarsholm N C
CORPORATE SOURCE: Health Care Discovery, Novo Nordisk A/S, Novo Alle 1, DK 2880, Bagsvaerd, Denmark.
SOURCE: Journal of molecular biology, (2000 Oct 20) 303 (2) 161-9. Journal code: 2985088R. ISSN: 0022-2836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001106

AB Within the class of insulin and insulin-like growth factor receptors, detailed information about the molecular recognition event at the hormone-receptor interface is limited by the absence of suitable co-**crystals**. We describe the use of a biologically active insulin derivative labeled with the NBD fluorophore (B29NBD-insulin) to characterize the mechanism of reversible 1:1 complex formation with a fragment of the insulin receptor ectodomain. The accompanying 40 % increase in the fluorescence quantum yield of the label provides the basis for a dynamic study of the hormone-receptor binding event. Stopped-flow fluorescence experiments show that the kinetics of complex formation are biphasic comprising a bimolecular binding event followed by a conformational change. Displacement with excess unlabeled insulin gave monophasic kinetics of dissociation. The rate data are rationalized in terms of available experiments on mutant receptors and the X-ray structure of a non-binding fragment of the receptor of the homologous insulin-like growth factor (**IGF-1**).


L8 ANSWER 31 OF 41 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:327891 BIOSIS

DOCUMENT NUMBER: PREV200000327891
TITLE: Protein metabolism in patients with chronic renal failure: Role of uremia and dialysis.
AUTHOR(S): Lim, Victoria S. [Reprint author]; Kopple, Joel D.
CORPORATE SOURCE: Department of Internal Medicine, University of Iowa Hospitals, 200 Hawkins Avenue, Iowa City, IA, 52242, USA
SOURCE: Kidney International, (July, 2000) Vol. 58, No. 1, pp. 1-10. print.
CODEN: KDYIA5. ISSN: 0085-2538.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Aug 2000
Last Updated on STN: 7 Jan 2002

AB Individuals with chronic renal failure (CRF) have a high prevalence of protein-energy malnutrition. There are many causes for this condition, chief among which is probably reduced nutrient intake from anorexia. In nondialyzed patients with CRF, energy intake is often below the recommended amounts; in maintenance dialysis patients, both dietary protein and energy intake are often below their needs. Although a number of studies indicate that rats with CRF have increased protein catabolism in comparison to control animals, more recent evidence suggests that increased catabolism in CRF rats is largely if not entirely due to acidemia, particularly if these animals are compared to pair-fed control rats. Studies in **humans** with advanced CRF also indicate that acidemia can cause protein catabolism. Indeed, nitrogen balance studies and amino acid uptake and release and isotopic kinetic studies indicate that in nondialyzed individuals with CRF, who are not acidemic, both their ability to conserve body protein when they ingest low protein diets and their dietary protein requirements appear to be normal. For patients undergoing maintenance hemodialysis or chronic peritoneal dialysis, dietary protein requirements appear to be increased. The increased need for protein is due, in part, to the losses into dialysate of such biologically valuable nitrogenous compounds as amino acids, peptides, and proteins. However, the sum of the dietary protein needs for CRF patients (of about 0.60 g/kg/day) and the dialysis losses of amino acids, peptides and proteins do not equal the apparent dietary protein requirements for most maintenance dialysis patients. This discrepancy may be due to a chronic state of catabolism in the clinically stable maintenance dialysis patient that is not present in the clinically stable nondialyzed individual who has advanced CRF. Possible causes for such a low grade catabolic state include resistance to anabolic hormones (for example, insulin, **IGF-1**) and a chronic inflammatory state associated with increased levels of pro-inflammatory cytokines.

L8 ANSWER 32 OF 41 MEDLINE on STN
ACCESSION NUMBER: 1999263104 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10325399
TITLE: Modelling of the disulphide-swapped isomer of **human insulin-like growth factor-1**: implications for receptor binding.
AUTHOR: Gill R; Verma C; Wallach B; Urso B; Pitts J; Wollmer A; De Meyts P; Wood S
CORPORATE SOURCE: Department of Biochemistry, School of Biological Sciences, University of Southampton, 6 Bassett Crescent East, Southampton SO16 7PX, UK.
SOURCE: Protein engineering, (1999 Apr) 12 (4) 297-303.
Journal code: 8801484. ISSN: 0269-2139.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990730
Last Updated on STN: 19990730
Entered Medline: 19990716

AB **Insulin-like growth factor-1** (**IGF-1**) is a serum protein which unexpectedly folds to yield two stable tertiary structures with different disulphide connectivities; native **IGF-1** [18-61,6-48,47-52] and **IGF-1** swap [18-61,6-47, 48-52].

Here we demonstrate in detail the biological properties of recombinant **human** native **IGF-1** and **IGF-1** swap secreted from Saccharomyces cerevisiae. **IGF-1** swap had a approximately 30 fold loss in affinity for the **IGF-1** receptor overexpressed on BHK cells compared with native **IGF-1**.The parallel increase in dose required to induce negative cooperativity together with the parallel loss in mitogenicity in NIH 3T3 cells implies that disruption of the **IGF-1** receptor binding interaction rather than restriction of a post-binding conformational change is responsible for the reduction in biological activity of **IGF-1** swap. Interestingly, the affinity of **IGF-1** swap for the insulin receptor was approximately 200 fold lower than that of native **IGF-1** indicating that the binding surface complementary to the insulin receptor (or the ability to attain it) is disturbed to a greater extent than that to the **IGF-1** receptor. A 1.0 ns high-temperature molecular dynamics study of the local energy landscape of **IGF-1** swap resulted in uncoiling of the first A-region alpha-helix and a rearrangement in the relative orientation of the A- and B-regions. The model of **IGF-1** swap is structurally homologous to the NMR structure of insulin swap and CD spectra consistent with the model are presented. However, in the model of **IGF-1** swap the C-region has filled the space where the first A-region alpha-helix has uncoiled and this may be hindering interaction of Val44 with the second insulin receptor binding pocket.

L8 ANSWER 33 OF 41 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:440123 CAPLUS
DOCUMENT NUMBER: 129:118051
TITLE: A novel mutation affecting the interdomain link region of the growth hormone receptor in a Vietnamese girl, and response to long-term treatment with recombinant **human** insulin-like growth factor-I and luteinizing hormone-releasing hormone analog
AUTHOR(S): Walker, J. L.; Crock, P. A.; Behncken, S. N.; Rowlinson, S. W.; Nicholson, L. M.; Boulton, T. J. C.; Waters, M. J.
CORPORATE SOURCE: School of Paediatrics, University of New South Wales, Randwick, 2031, Australia
SOURCE: Journal of Clinical Endocrinology and Metabolism (1998), 83(7), 2554-2561
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A Vietnamese girl with Laron syndrome has been treated with recombinant **human** insulin-like growth factor-I for 4 yr from age 11.28 yr. Her height SD score increased from -6.3 to -4.7 without acceleration of bone age. Isolated breast development progressed despite pubertal suppression with LH-releasing hormone analog, which was stopped after 3 yr because of growth deceleration. Facial coarsening was documented with serial photographs. Sequencing and in vitro anal. identified a homozygous base pair substitution in exon 6 of the proband's GH receptor (GHR), which changed amino acid 131 from proline to glutamine (P131Q) and disrupted GH binding. Both the P131Q-mutated **human** GHR and wild-type (wt.) hGHR were transiently expressed in COS-1 cells, as demonstrated by Western blotting, but the P131Q-transfected cells did not bind 125I-hGH. Similarly, FDC-P1 cells transfected with wthGHR bound 125I-hGH with high affinity and proliferated in response to GH, whereas the P131Q hGHR cells did neither. In CHO-K1 cells cotransfected with wthGHR and the Egr-1 promoter linked to a luciferase reporter gene, GH evoked a 2.14.+-.0.21-fold increase in luciferase activity, but there was no response in the cells carrying the P131Q hGHR mutation. From examn. of the **crystal** structure of the GHR, we suggest that the P131Q mutation disrupts the interdomain link between the extracellular domains of the GHR, causing a conformational change that results in disruption of the GH binding site.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 34 OF 41 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

ACCESSION NUMBER: 1998:502414 SCISEARCH
THE GENUINE ARTICLE: ZW273
TITLE: The protein kinase ABC's of signal transduction as targets for drug development
AUTHOR: Glazer R I (Reprint)
CORPORATE SOURCE: GEORGETOWN UNIV, MED CTR, RM W318, RES BLDG, 3970 RESERVOIR RD NW, WASHINGTON, DC 20007 (Reprint); DEPT PHARMACOL, WASHINGTON, DC 20007; VINCENT T LOMBARDI CANC RES CTR, WASHINGTON, DC 20007
COUNTRY OF AUTHOR: USA
SOURCE: CURRENT PHARMACEUTICAL DESIGN, (JUN 1998) Vol. 4, No. 3, pp. 277-290.
Publisher: BENTHAM SCIENCE PUBL BV, PO BOX 1673, 1200 BR HILVERSUM, NETHERLANDS.
ISSN: 1381-6128.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 207

*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Signal transduction plays a key regulatory role in the growth and metastatic potential of tumor cells. These signaling pathways form an interconnecting grid that serves to regulate the homeostatic, survival and invasive functions of the cell. Among the key regulatory molecules in these pathways are the serine/threonine-protein kinases A, B and C, also known respectively as cyclic AMP-dependent protein kinase (PKA), Akt (PKB) and protein kinase C (PKC). These protein kinases modulate pathways associated with tumor proliferation, cell survival and multidrug resistance, and at a molecule level are likely to serve as effective targets for drug design. The unique structural features of each protein kinase have been deduced from their **crystallographic** structures and form unique opportunities for structure-based drug design. In addition, these protein kinases are potentially important targets for antisense oligonucleotide therapy, and therefore may provide a means of selectively inhibiting tumor proliferation and inducing apoptosis with minimal nonspecific cytotoxicity.

L8 ANSWER 35 OF 41 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 1999040448 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9823114
TITLE: The behaviour and proliferation of **human** dental pulp cell strains in vitro, and their response to the application of platelet-derived growth factor-BB and **insulin-like growth factor-1**.
AUTHOR: Denholm I A; Moule A J; Bartold P M
CORPORATE SOURCE: Department of Dentistry, University of Queensland, Brisbane, Australia.
SOURCE: International endodontic journal, (1998 Jul) 31 (4) 251-8.
Journal code: 8004996. ISSN: 0143-2885.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Dental Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981124

AB **Human** dental pulp fibroblast strains were established from explants of dental pulps using identical culture techniques. To determine proliferative activity, a 3H-thymidine uptake and a **crystal** violet dye-binding assay were performed at passage numbers seven and eight. Assays were performed in the presence of either 0% fetal calf serum (FCS), 0.2% FCS or 10% FCS. Considerable variation in the overall proliferative activity of the different pulp cell strains (when averaged over all other variables) was noted. All dental pulp cell strains demonstrated significantly different proliferative activity from each other. In addition, the level of proliferative response and 3H-thymidine incorporation decreased as the passage number of the cells increased. This was in accordance with the findings of Tardieu-Moreau et al. (1992). It is proposed that the differences in proliferative activity are most

likely attributable to inherent variability within the established pulp cell strains. Platelet derived growth factor-BB (PDGF-BB) and **insulin-like growth factor-1** (**IGF-1**) were added to the **human** pulp cells both separately and in combination. All of the pulp cells exhibited increased proliferative activity in the presence of the growth factors with the combination of PDGF-BB/**IGF-1** having the greatest mitogenic effect. There was also significant variability in the level of response of all pulp cell strains to the different growth factors. This study identified significant variability in the responsiveness to the growth factors between the pulp cell strains when the results of the 3H-thymidine and dye binding assays were compared. These findings reinforce the thesis that different assay procedures may also influence the findings of biological investigations involving the **human** dental pulp. The results of this study confirm that when comparing the findings of different in vitro studies involving **human** pulp cells, variations in experimental data can be strongly influenced by the pulp cell strain used and the culture technique employed. Indeed, studies of **human** pulp cell proliferation using pulp cells which are not of the same transfer number may not be relevant.

L8 ANSWER 36 OF 41 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 1998078580 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9416620
TITLE: **Crystallization** of the first three domains of the **human insulin-like growth factor-1** receptor.
AUTHOR: McKern N M; Lou M; Frenkel M J; Verkuylen A; Bentley J D; Lovrecz G O; Ivancic N; Elleman T C; Garrett T P; Cosgrove L J; Ward C W
CORPORATE SOURCE: CSIRO Division of Molecular Science, Parkville, Victoria, Australia.
SOURCE: Protein science : a publication of the Protein Society, (1997 Dec) 6 (12) 2663-6.
Journal code: 9211750. ISSN: 0961-8368.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980224
Last Updated on STN: 20000303
Entered Medline: 19980210
AB The **insulin-like growth factor-1** receptor (IGF-1R) is a tyrosine kinase receptor of central importance in cell proliferation. A fragment (residues 1-462) comprising the L1-cysteine rich-L2 domains of the **human** IGF-1R ectodomain has been overexpressed in glycosylation-deficient Lec8 cells and has been affinity-purified via a c-myc tag followed by gel filtration. The fragment was recognized by two anti-IGF-1R monoclonal antibodies, 24-31 and 24-60, but showed no detectable binding of **IGF-1** or IGF-2. Isocratic elution of IGF-1R/462 on anion-exchange chromatography reduced sample heterogeneity, permitting the production of **crystals** that diffracted to 2.6 A resolution with cell dimensions a = 77.0 A, b = 99.5 A, c = 120.1 A, and space group P2(1)2(1)2(1).

L8 ANSWER 37 OF 41 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1997:340699 BIOSIS
DOCUMENT NUMBER: PREV199799639902
TITLE: Fluoride treatment increased serum **IGF-1**, bone turnover, and bone mass, but not bone strength, in rabbits.
AUTHOR(S): Turner, C. H. [Reprint author]; Garetto, L. P.; Dunipace, A. J.; Zhang, W.; Wilson, M. E.; Grynpas, M. D.; Chachra, D.; McClintock, R.; Peacock, M.; Stookey, G. K.
CORPORATE SOURCE: Indiana Univ. Sch. Med. Dent., 541 Clinical Drive, Suite 600, Indianapolis, IN 46202, USA
SOURCE: Calcified Tissue International, (1997) Vol. 61, No. 1, pp. 77-83.
CODEN: CTINDZ. ISSN: 0171-967X.

DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Aug 1997
Last Updated on STN: 11 Aug 1997

AB We hypothesized that fluoride partly acts by changing the levels of circulating calcium-regulating hormones and skeletal growth factors. The effects of oral fluoride on 24 female, Dutch-Belted, young adult rabbits were studied. The rabbits were divided into two study groups, one control and the other receiving about 16 mg fluoride/rabbit/ day in their drinking water. After 6 months of fluoride dosing, all rabbits were euthanized and bone and blood samples were taken for analyses. Fluoride treatment increased serum and bone fluoride levels by over an order of magnitude (P lt 0.001), but did not affect body weight or the following serum biochemical variables: urea, creatinine, phosphorus, total protein, albumin, bilirubin, SGOT, or total alkaline phosphatase. No skeletal fluorosis or osteomalacia was observed histologically, nor did fluoride affect serum PTH or Vitamin D metabolites (P gt 0.4). BAP was increased 37% (P lt 0.05) by fluoride; serum TRAP was increased 42% (P lt 0.05); serum **IGF-1** was increased 40% (P lt 0.05). Fluoride increased the vertebral BV/TV by 35% (P lt 0.05) and tibial ash weight by 10% (P lt 0.05). However, the increases in bone mass and bone formation were not reflected in improved bone strength. Fluoride decreased bone strength by about 19% in the L5 vertebra (P lt 0.01) and 25% in the femoral neck (P lt 0.05). X-ray diffraction showed altered mineral **crystal** thickness in fluoride-treated bones (P lt 0.001), and there was a negative association between **crystal** width and fracture stress of the femur (P lt 0.02). In conclusion, fluoride's effects on bone mass and bone turnover were not mediated by PTH. **IGF-1** was increased by fluoride and was associated with increased bone turnover, but was not correlated with bone formation markers. High-dose fluoride treatment did not improve, but decreased, bone strength in rabbits, even in the absence of impaired mineralization.

L8 ANSWER 38 OF 41 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 96083042 EMBASE
DOCUMENT NUMBER: 1996083042
TITLE: Mechanisms of tumor-induced hypoglycemia with intraabdominal hemangiopericytoma.
AUTHOR: Chung J.; Henry R.R.
CORPORATE SOURCE: VA Medical Center, 3350 La Jolla Village Drive,San Diego, CA 92161, United States
SOURCE: Journal of Clinical Endocrinology and Metabolism, (1996) 81/3 (919-925).
ISSN: 0021-972X CODEN: JCEMAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The association of hypoglycemia with nonislet cell tumors is well recognized and in nearly all instances has been related to the production of hormones with insulin-like activity. To determine the mechanism of such tumor-induced hypoglycemia and the response to pharmacological intervention, we studied a 54-yr-old man with refractory hypoglycemia and a large intraabdominal hemangiopericytoma. During a supervised fast, plasma glucose decreased to 2.2 mmol/L. Circulating insulin (<7 pmol/L), C peptide (<0.04 nmol/L), and GH levels (<0.6 .mu.g/L) were all undetectable, **insulin-like growth factor 1** (IGF-I; 5 nmol/L) was low, IGF-II was in the normal range (87 nmol/L), and free IGF-II and big IGF-II (E1-21 fragment) were elevated at 18 and 142 nmol/L, respectively. On another day, after maintaining euglycemia overnight with a 20% dextrose infusion, a euglycemic (5.0-5.5 mmol/L) glucose clamp study using [3-3H]glucose tracer infusion combined with arteriovenous leg catheterization was performed in the postabsorptive basal state and during 3 h of **crystalline** somatostatin infusion (0.08-0.24 pmol/kg .cntdot. min). In the postabsorptive state at euglycemia, free IGF-II and big IGF-II remained elevated at 16 and 162 nmol/L, respectively. Whole body glucose disposal

was elevated at 21.1 .mu.mol/kg .cntdot. min, whereas the rate of glucose infusion was 12.1 .mu.mol/kg .cntdot. min, and hepatic glucose output was 7.8 .mu.mol/kg .cntdot. min. The leg arterio-venous plasma glucose difference was increased at 0.6 mmol/L, as was leg glucose uptake at 203.9 .mu.mol/min. After 3 h of somatostatin infusion, both free and big IGF-II decreased by 85-40% to 10 and 102 nmol/L, respectively. Whole body glucose disposal also decreased to near normal (12.8 .mu.mol/kg .cntdot. min), whereas leg arterio-venous plasma glucose difference and leg glucose uptake became negligible. The plasma glucose level remained at 5.0-5.5 mmol/L despite a marked fall in hepatic glucose output to 2.9 .mu.mol/kg .cntdot. min and a decrease in glucose infusion rate to 8.7 .mu.mol/kg .cntdot. min. During somatostatin treatment, GH remained suppressed at less than 0.6 .mu.g/L, and glucagon decreased from 99 to 78 ng/L. In this patient with a hemangiopericytoma, hypoglycemia was associated with increased circulating insulin-like activity from elevated free and big IGF-II, which stimulated glucose uptake primarily into muscle tissue. A continuous infusion of **crystalline** somatostatin effectively reduced the elevated levels of IGF- II and glucose uptake, but was unable to adequately control hypoglycemia without the simultaneous infusion of exogenous glucose or glucagon.

L8 ANSWER 39 OF 41 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 95187565 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7881770
TITLE: Nerve growth factor increases the mitogenicity of certain growth factors for cultured **human** keratinocytes: a comparison with epidermal growth factor.
AUTHOR: Wilkinson D I; Theeuwes M J; Farber E M
CORPORATE SOURCE: Psoriasis Research Institute, Palo Alto, CA 94301.
SOURCE: Experimental dermatology, (1994 Oct) 3 (5) 239-45. Journal code: 9301549. ISSN: 0906-6705.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199504
ENTRY DATE: Entered STN: 19950425
Last Updated on STN: 20000303
Entered Medline: 19950411

AB Newborn foreskin and adult skin keratinocytes (KTs) were cultured in 24-well plates using keratinocyte basal medium (KBM) either alone or supplemented with epidermal growth factor (EGF) or nerve growth factor (NGF), plus one of the following: insulin (INS), insulin-like growth factors (**IGF**)**-1** or -2, transforming growth factor alpha (TGF alpha), basic fibroblast growth factor (bFGF). Culture was maintained until one group of cells reached about 30,000 cells/well, when cells were stained with **crystal** violet and the extracted dye used to quantify cell numbers. In some cases, cells were subjected to the hexosaminidase assay for enumeration. In KBM alone, EGF, **IGF-1**, IGF-2 and TGF alpha were mitogenic to newborn KTs. In addition, NGF increased the growth of adult KTs, possibly by mechanisms involving synergy with autocrine growth factors. EGF augmented the growth of newborn cells in the presence of each of the growth factors except TGF alpha, but adult cells exhibited only additive effects. In the presence of **IGF-1** or IGF-2, NGF stimulated the growth of both newborn and adult cells by as much as 150% above purely additive increases in cell numbers. NGF amplifies the effects of most neurotrophic factors that are also KT mitogens and may therefore be significant in psoriatic lesions, where many of these factors are overexpressed, and in wound healing, in promoting KT growth.

L8 ANSWER 40 OF 41 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 95087493 EMBASE
DOCUMENT NUMBER: 1995087493
TITLE: Inhibition of bFGF and EGF-induced proliferation of 3T3 fibroblasts by extract of Pygeum africanum (Tadenan.RTM.).
AUTHOR: Paubert-Braquet M.; Monboisse J.C.; Servent-Saez N.; Serikoff A.; Cave A.; Hocquemiller R.; Dupont Ch.; Fourneau C.; Borel J.P.
CORPORATE SOURCE: Bio-Inova, Laboratoire de Recherche, 48-52, rue de la

Gare,78370 Plaisir, France
SOURCE: Biomedicine and Pharmacotherapy, (1994) 48/SUPPL. 1 (43S-47S).
ISSN: 0753-3322 CODEN: BIPHEX
COUNTRY: France
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 028 Urology and Nephrology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB An extract of Pygeum africanum bark (Tadenan.RTM.) is prescribed for older men suffering from micturitional difficulties due to benign prostatic hyperplasia (BPH). Its mechanism of action is not completely understood. Basic fibroblast growth factor (bFGF) probably plays a role in the development of BPH. We have examined the effects of P africanum extract on basal cell proliferation and on the proliferation induced by bFGF, epidermal growth factor (EGF) and **insulin-like growth factor-1** (**IGF-1**). The proliferation of 3T3 fibroblasts was measured by the incorporation of tritiated methylthymidine and staining nuclei with **crystal** violet. P africanum extract slightly inhibited the basal growth of fibroblasts. However, it had a much larger inhibitory effect on cell proliferation induced by bFGF with 0.5 .mu.g/ml, and the effect was significant at 1 .mu.g/ml. Pygeum africanum extract also inhibited cell proliferation induced with EGF, but to a lesser extent. This suggests that the therapeutic effect of P africanum extract may be partly due to inhibition of cell growth induced by certain growth factors.

L8 ANSWER 41 OF 41 MEDLINE on STN
ACCESSION NUMBER: 83079574 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6756944
TITLE: Insulin-like growth factors, **IGF-1**, IGF-2 and somatomedin C trigger cell proliferation in mammalian epithelial cells cultured in a serum-free medium.
AUTHOR: Reddan J R; Dziedzic D C
CONTRACT NUMBER: EY-00362 (NEI)
SOURCE: Experimental cell research, (1982 Dec) 142 (2) 293-300.
Journal code: 0373226. ISSN: 0014-4827.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198302
ENTRY DATE: Entered STN: 19900317
Last Updated on STN: 19970203
Entered Medline: 19830225

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